

8650

BILE
ITS TOXICITY AND RELATION
TO DISEASE

By

O. H. HORRALL, M.D., PH.D., F.A.C.S.

Department of Physiology, The University of Chicago

025123

THE UNIVERSITY OF CHICAGO PRESS
CHICAGO ILLINOIS

**COPYRIGHT 1938 BY THE UNIVERSITY OF CHICAGO. ALL RIGHTS
RESERVED. PUBLISHED APRIL 1938. COMPOSED AND PRINTED BY
THE UNIVERSITY OF CHICAGO PRESS, CHICAGO, ILLINOIS, U.S.A.**

FOREWORD

THE bile, with its striking characteristics of color and taste, attracted the attention of the ancients and has held the interest of physicians and scientists to the present day. In no other subject in medicine have we a more complete record of the contrasting methods of approach to natural phenomena through the ages. Thus, the story of bile comes near being the natural history of the evolution of the scientific method in medicine. To the ancients, dealing mainly with mere ideas, the role of the bile in health and disease presented scarcely any problem. For could not cause and effect in nature be determined by pure logic? To the physician and the laboratory investigator of today, questioning all theories and ever rechecking reported facts, bile presents urgent problems of increasing complexity. The winnowing of the literature on the bile problem is an enormous task, even for a scholar with experience both in clinical and laboratory research. But when completed with the breadth, objectivity, clarity, and critical acumen disclosed in this monograph, it is a genuine service to medical science. This monograph raises more questions than it settles, despite its analysis of some two thousand years of speculation, observation, and experimentation on bile. It is a report of progress, a progress rendered possible by the advances in the sciences of biology, chemistry, and physics. Some of the more important questions confronting today's investigator on the bile problem could not even have been conceived in the days of Hippocrates and of Galen. This monograph should help to conserve the time of fellow-workers by its compilation of proved and of probable facts, by its charting of blind alleys, and by its indexes of methods of further experimental work in regions requiring more light.

A. J. CARLSON

UNIVERSITY OF CHICAGO
December 1937

PREFACE

THIS monograph endeavors to summarize and analyze the physiologic and toxic actions of bile as revealed by past observations and experiments. It is hoped that this will stimulate further research, so much needed in this field, and that it will aid the physician in the recognition and rational therapy of various conditions with which jaundice is associated.

Much has been written on (the clinical significance of bile, especially its relation to jaundice), but no critical summary of our modern knowledge of the composition of bile and its relation to disease is available. The literature is voluminous. Some of it is based on clinical observations and laboratory investigations. Part of it belongs to philosophy, mythology, and quackery. The latter can be discarded without difficulty, but the sifting of the serious literature is a difficult task where findings are divergent, and in many instances we must be satisfied with marshaling the pros and cons, leaving the decision to the future investigator.

The bibliography is intended to conserve the time and labor of workers in this field. It seems extensive; but in general only the more significant publications have been included, particularly those pointing toward new lines of investigation. In recent years good work has been done on bile in practically every country, but the various languages in which this work has been published present difficulties.

Grateful acknowledgments are due to the *Archives of Internal Medicine* and to the *Journal of Laboratory and Clinical Medicine* for permission to reproduce portions of articles.

I am particularly indebted to Professor A. J. Carlson for his advice, encouragement, and helpful guidance during my thirteen years of experimental work in the Department of

Physiology of the University of Chicago and for his valuable suggestions in the writing of this monograph.

The writer is grateful to Ruby Arnett Horrall for her aid in the preparation of the manuscript and the bibliography, to Miss Mary D. Alexander for her painstaking handling of the production of the book, and to my associates who have aided in the experimental work.

This work, originally completed in 1932, has been re-written and revised in the light of the more recent work up to July, 1937.

The oldest-known word for bile is given on the title-page. This word was found in the Ebers Papyrus, which was written about 1600 B.C.

O. H. HORRALL

TABLE OF CONTENTS

| CHAPTER | PAGE |
|--|------|
| I. HISTORY OF BILE | 1 |
| II. EXPERIMENTAL HISTORY | 7 |
| III. METHODS OF INVESTIGATION | 18 |
| IV. CONSTITUENTS OF BILE | 20 |
| V. ORIGIN AND FATE OF BILE | 41 |
| VI. TOXICITY OF BILE ACIDS | 60 |
| VII. NONTOXICITY OF BILE PIGMENTS | 73 |
| VIII. TOXICITY OF OTHER CONSTITUENTS OF BILE | 94 |
| IX. CONCENTRATION OF BILE IN THE BLOOD | 106 |
| X. THE EFFECT OF BILE ON THE BLOOD CELLS | 112 |
| XI. BLEEDING IN JAUNDICE | 124 |
| XII. ACTION OF BILE ON THE NERVOUS SYSTEM | 137 |
| XIII. ACTION OF BILE ON THE HEART AND BLOOD PRESSURE | 145 |
| XIV. ACTION OF BILE ON SKELETAL MUSCLE | 160 |
| XV. EXCRETION OF BILE IN THE URINE AND ITS TOXIC ACTION | 165 |
| XVI. ACTION OF BILE ON THE <u>UTERUS</u> | 178 |
| XVII. ACTION OF BILE ON THE GASTROINTESTINAL SYSTEM | 180 |
| XVIII. ACTION OF BILE ON BACTERIA AND TOXINS | 196 |
| XIX. BILE AND ACUTE PANCREATITIS | 204 |
| XX. WHY BILE DOES NOT CAUSE NECROSIS OF THE GALL- BLADDER | 208 |
| XXI. BILE PERITONITIS | 210 |
| XXII. BILE RETENTION: ICTERUS | 225 |
| XXIII. PHYSIOLOGIC JAUNDICE | 249 |
| XXIV. JAUNDICE CAUSED BY EXTRAHEPATIC OBSTRUCTION | 252 |
| XXV. BILE LOSS | 262 |
| XXVI. THERAPEUTIC EFFECTS OF BILE ACIDS | 269 |
| XXVII. GENERAL CONCLUSIONS | 279 |
| BIBLIOGRAPHY | 282 |
| INDEX | 409 |

CHAPTER I

HISTORY OF BILE

THE idea that bile is toxic is almost as old as literature itself. The writings of the ancients contain numerous references to bile; the earliest-known reference is in an Egyptian sacerdotal papyrus¹ written about 1300 B.C. (511),² where it is advised for use in enemas. The word *bile* signifies poison. The old Hebrew word is *rosh*, which means poison. The Greek word is *χολή*,³ which means yellow and, metamorphically, indignation, anger, and wrath. This word has cognates in the Sanscrit and Slav languages. The Latin word *bilis* means bile, or bitterness (Pliny). *Galla*, which means gallnut or oak apple, is also used for bile. Still another Latin word, *cholera*, was used for bile until the beginning of the eighteenth century. This word is really a translation from the previously given Greek word. The Old French, Dutch, German, Old Norse, Anglo-Saxon, and Middle English words are similar; and all have practically the same meaning. The Greek word *χολή*³ was used as early as

¹ The translation here referred to has been questioned by some Egyptologists.

² Numbers in parentheses refer to bibliography.

³ Galeni *De atrabile*:

Yellow bile=normal bile=neutral bile

χολέρα = *cholera* = bile, jaundice

χολέρικος = *cholericus* = bilious, jaundiced

μελαςχολη = *atra bilis* or *nigra bilis* = black bile, melancholy or dejection, "supposed an abundant source of disease"

Biliosus (adj.)=full of bile, bilious, or hypochondriac

Galeni *De natura hominis*:

Body of man contains blood, *pituita*, and two kinds of bile, yellow and black. . . . Disease takes place if either kind of bile is in excess or deficient, or if not duly united. Bile predominates in summer, and *atrabilis* in the autumn.

Latin word *fel* (n.) is translated as gallbladder, bile, or gall; also as bitterness, anger, or wrath.

700 B.C. in the writings of Archilochus; in 484 B.C. by Aeschylus; in 450 B.C. by Sophocles; and in 441 B.C. by Euripides. To Hippocrates, 430 B.C., it meant black bile or diseased bile. According to a proverb recorded by Diphilus in 320 B.C., it was the custom of the mother to put gall to the nipple when the child was to be weaned, thus causing a disgust. By this time it had become a definitely established belief that bile was to be avoided.⁴

Bilis, meaning bile, was used by Cato; *subfusio luridae bilis*, the jaundiced (overflowing with bile), by Anneus Seneca; *cholera*, for jaundice, by Celsus; *galla*, for gall, by Pliny, and for inferior harsh wine, by Lucilius. Virgil expressed the prevalent idea that bile is poisonous in: *Sagittam armatam saevi Parthus quam felle veneni . . . torsit*.⁵ In the medicine of the ancient Hindus, bile played an important part. The *tridoṣa* doctrine is explained in the sacred books of the East: Kausikasutra, and various Vedas dating from before 1100 B.C. to not later than the second century before Christ. In Buddhist medicine the three faults are *vāyu*, *pitta*, and *kapha*—and bile and mucus. The *doṣa* are responsible for all the morbidities of the body and, so long as they remain in their proper relation and balance, will not weaken the body or produce disease. According to these books, the bile of fish is poisonous (*sus kalpa*) (Müller, Dasgupta).

It is natural that even the layman should be aware of bile because of its characteristic color, odor, and taste and because of its presence in almost all forms of animal life. Animal food has been used for human consumption since the earliest recorded time; and all through the ages references have been

⁴ Bile is used in various religious purification rites and ceremonies, either to entice the good spirits or to drive away the evil (Willoughby). The religious uses of bile would require a large amount of space, which is not available in a work of this kind.

The Kaffirs drink bile and seem to enjoy it, according to Harley (766, p. 18).

In Abyssinia, bile is drunk as a tonic for the stomach and is considered a luxury; see Smith (1783).

The Chinese add bile to their salad; see Haller (747, p. 18).

⁵ "An arrow armed with gall, of cruel poison, a Parthian has shot," from Virgil *Aeneid* xii. 857.

made to unfit or unclean food, especially to that which had been contaminated by bile. Probably most of these conclusions were drawn because of the peculiar taste and color produced by bile when brought in contact with meat. The taste is very persistent and pungent. The color is characteristic, penetrating, and exceedingly difficult to remove or to fade, particularly from animal tissue.

Hippocrates,⁶ 430 B.C., based his whole system of medicine on the assumption that bile was the common cause of disease—in fact, he believed it to be the cause of practically all illness. Widespread interest was aroused by his teachings. Centuries later, Galen, born A.D. 131, based his voluminous medical works on the same assumption. He believed that virtually all the discomforts and ailments of the human body and mind were caused by bile—its varying location, character, quality, and quantity. Accordingly, he founded, or rather re-established, a system of medicine with bile as the key to all diseases. He thought that yellow bile caused many infirmities and that black bile, a poison, produced chronic suffering, apoplexy, convulsions, and melancholia.

This teaching spread throughout Greek, Roman, and Arabic medicine; and numerous systems were built upon it. For almost three thousand years the idea that bile was toxic and caused disease prevailed. It took the daring and indomitable work of numerous clear, unfettered thinkers of the Middle Ages to emancipate medicine from these dogmatic views. Galen's works were the law, and no one dared to re-

⁶Hippocrates (823):

1. *De morbis* i. 2: All disease arises from bile or phlegm.

2. *De natura hominis* iv. 6. 39:

Four humors: blood, phlegm, yellow bile, and black bile.

Disease arises from improper balance or excess or defect of any of these.

3. *De morbis* iv. 33. (7) 540: Four humors: blood from the heart; phlegm from the head; yellow bile from the liver; and dropsy (water) from the spleen.

Galen and Hippocrates (Coxe):

The four cardinal humors are *blood*, *pituita* (phlegm), *bile* (yellow bile), and *melancholy* (black bile).

Changes in these humors cause a large proportion of morbid actions or diseases.

fute or question them, under penalty of death.⁷ When once the works were refuted, the references to bile became few and implied charlatanism. Hence, for a time, few ideas were expressed as to the action of bile or its toxicity until the latter part of the eighteenth century. However, early in the sixteenth century Paracelsus completely rejected the idea that bile had pathogenic properties. He thought it a useless refuse, a meaningless excretion. Van Helmont, in 1648, taking a middle course, declared that bile was nonpathogenic—indeed “the very balsam of life, a noble juice which could not cause disease.” But it was Sydenham, in 1669, following the revolutionary work of William Harvey in England in 1628, who first expressed the view that jaundice was a symptom and accompanied very different diseases.

Literature on biliary and melancholy humors continued to appear during the first half of the eighteenth century. Nuck, 1723, stated that diseases were due to *deficit bilis*, *contra quantitate nimia*, and *contra quantitate vitiosa*. He explained that various diseases were due to too little bile, to too thick bile, and mentioned *diarrhoea biliosa*, *dysenteriam* and *icterus* and advised *cholagugues*. In 1747 Quesnay wrote chapters on biliary and melancholy humors. He said that the biliary humor dissolved all other humors and actually got into the blood; that bile was, of all humors, the most corruptible; that it excited the intestine and caused itself to be expelled because of its *acrimonie*, and was the cause of dysenteries and diarrhea. He declared black bile, *atrabilis*, the melancholy humor, to be abundant in different excretions and suppuration, and the cause of many diseases; and maintained that

⁷ Paracelsus, in 1527, burned the works of Galen; and the authorities forced him to leave Basel.

Vesalius, 1543, published an anatomy contrary to the Galenical traditions, and the persecution that followed caused him to burn publicly his own books and to quit teaching.

Harvey, 1642, was working on the circulation of the blood when his chambers in Whitehall were invaded by parliamentary troops, who destroyed his experimental work and his manuscripts (Garrison, *History of Medicine*, p. 245).

temperament was dependent on the humor which was temporarily predominant.

Many views as to diseases of the liver appeared from the time of van Helmont, 1648, up to the beginning of the nineteenth century, when intensive work was begun on the chemistry of bile by Thenard, 1805; Berzelius, 1814; followed by Tiedemann and Gmelin, 1826; and Demarçay, 1838. Various diseases of the liver had been described, and to a certain extent the pathology of the liver had been worked out; but practically nothing had been done with bile until the investigation of the chemical side of the question was started early in the nineteenth century. In 1852 Budd (299) wrote about the excessive and diminished secretion of bile, its altered quality, and unhealthy states. He described many kinds of bile found at autopsy and attributed the changes to the particular diseases.

It is significant, however, that Berzelius said that more work had been done on bile previous to 1800 than on any other animal fluid. His reviews of the chemistry of bile from 1800 to 1842 cited the work of Fourcroy and Vauquelin, who, in 1790, made the first chemical analysis of bile. In his own analysis in 1808, he identified some of its constituents. In 1841 he presented a new analysis, in which he named numerous constituents; many of these names have been retained to the present time. Some substances were incorrectly named chemically, and others have been renamed for various reasons. Meanwhile, Demarçay found a method of removing mucus from bile which made it easier to work with other components. The empirical formulas for some of the acids were worked out by Demarçay and Dumas.

Beginning with the discovery of *acid glycocholique* by von Gorup-Besanez, 1846, the idea of the composition of bile entirely changed. There had been some evidence that bile was not a single chemical substance. This discovery opened the entire field for the investigation of the composition of bile. Then came the notable works of Strecker, in 1848, with bile

acids; Marsson, in 1849, with the identification of various constituents of bile; and Hoppe-Seyler, in 1862, with the chemistry of bile. It had been established by that time that bile is not a simple chemical substance but a very complex one, or rather a mixture of a great variety of chemical substances. Some of these substances are simple, while others are very intricate and even now have unknown chemical formulas. The present writer has been unable to find any one article that attempts to list completely the various constituents of bile.

Many substances found in bile are modified by their interrelation with other substances and probably act as "symbiotic" materials; for example, if bile acids are removed from bile, bilirubin and cholesterol are precipitated. It would appear that any work on bile must take into account this complexity. New substances may be added to bile, or it may be altered at different times and under different conditions or may be modified in various diseases. At the present time we do not know the actual complete chemistry of normal bile; and practically nothing is known of its chemistry under pathologic conditions. Only a few abnormal substances have been isolated from bile; probably many occur in it under various conditions.

The word *bile*, in much of the present research work, refers to the fluid that comes from the liver of an animal by way of the bile passages and that has the characteristic color. Bile may contain very little bile salts, or it may contain as much as 20 per cent. It is commonly called bile if it has the essential color.

RÉSUMÉ

Bile has been known during all recorded time. It was believed to be the cause of all diseases, both physical and mental, until recently. Only during the past century has its real identity become known and fruitful research been started.

CHAPTER II

EXPERIMENTAL HISTORY

FIRST EXPERIMENT

THE first biologic experiments with bile were made by Deidier in 1722. Bile was obtained from patients who had died of the plague at Marseilles, and was injected intravenously into dogs. All the dogs died quickly. Bile was also placed on open wounds in dogs, and they all died; when given by mouth, the bile caused no illness. Deidier concluded that bile was toxic when given intravenously.

ANIMAL EXPERIMENTS

It was found by Magendie, 1824, that when 1 gm. of bile was injected into the crural vein of dogs they died within a few moments. The same quantity injected slowly into the vena porta caused no disturbance. He concluded that the intravenous injection of bile was invariably fatal. Nevertheless, he rightly said that, in the present state of ignorance relative to the cause of disease, noxious properties were attributed to bile which it is far from possessing. Goupil, in 1838, injected 16 cc. of bile into the saphenous vein of a dog. There was some general agitation which appeared shortly after the injection, but the dog gradually recovered without any disturbance in health. Injection of the same quantity of whole bile into the vena porta was followed by no toxic symptoms. Up to this time, very little was known of the chemistry of bile, since only qualitative work had been done and few constituents had been identified. F. Bouisson, in 1843, repeating the work of Magendie, used human whole gallbladder bile and injected 6 cc. into the jugular of rabbits, causing the death of all. On dissection he found distension of the right heart and thrombosis of the pulmonary artery.

When the bile was filtered and then injected, the rabbits were temporarily sick with stupor and malaise but in a few hours became quite well again. He then concluded that impurities which could be filtered out caused the ill effects; that death was due to the mechanical blocking of the capillaries of the lung by substances which were suspended in the bile; and that bile itself was nontoxic. Henle also doubted the poisonous action of bile, and in 1847 stated that the widespread opinion that bile was poisonous had not been proved. He found that ox bile was an excellent preservative for the red corpuscles of the frog. Moleschott, 1852, removed the livers from frogs, which lived for some time afterward, but no chemical trace of bile acids was found in the blood, lymph, or urine.

In 1854 von Dusch began his experimental work with the various constituents of bile. Bile salts, chiefly the cholate portion, were very poisonous, according to his findings; but taurin and glycoll were not. Filtered ox bile was injected intravenously into rabbits, causing death in 2-3 minutes. Von Dusch made the first extensive study of the toxicity of bile salts (this will be referred to later in detail). Frerichs, in 1858, was the first to use mucus-free decolorized ox bile, concluding that bile was never fatal unless air was introduced into the vein. He also used sodium glycocholate and sodium taurocholate intravenously, and erroneously concluded that bile acids were converted into bile pigments.

In the same year Kühne proved that bile acids, as well as bile pigments, passed over into the urine in obstructive jaundice; that bile acids were not decomposed by the blood but were excreted by way of the kidneys unchanged; and that bile acids injected intravenously were likewise excreted. He concluded that intravenous bile caused the red cells to give off hematin, which was changed into bile pigment, and that the bile acids normally passed off with the feces and were not reabsorbed from the intestine.

In December, 1858, Valentin (634), in Frerichs' laboratory,

discovered the similarity between hematin crystals and bile-pigment crystals. Then Frerichs admitted the possibility of a relationship between bile pigment and blood pigment. Thus, for the first time was the source of bilirubin indicated. Frerichs (634), however, still maintained his theory that the colorless biliary acids were also convertible into bile pigment.

Bile acids (salts) were injected intravenously into dogs by Neukomm,¹ 1860, who, failing to recover bile acids from the urine, and finding bile pigments present chemically, concluded that the bile acids were changed into bile pigments in the blood stream and as such were excreted in the urine. He thought it possible that some special organ, such as the liver or pancreas, or that a reaction with fat, caused the change from bile acid to bile pigment.

Using dogs in some of the experiments, Betz,² 1862, placed ligatures about the vessels to and from the liver, and about the bile ducts, and observed the effect of the tightening of ligatures on the blood and bile flow. The liver was excised and placed in a bell-jar apparatus with manometers and infusion tubes which were connected with the liver vessels and bile ducts. The effects of variations in pressure of the inflowing solutions were observed, also the effect of occlusion of the vessels and ducts. He showed that even a slight pressure on the biliary duct, causing obstruction, was followed by a diminished portal blood flow; and he attributed the symptoms to mechanical, rather than to toxic, effect.

¹ Neukomm (1376), without anesthetic, injected 0.8 gm. of sodium glycocholate in 10 cc. of water into the crural vein of a dog. The urine was collected for 36 hours afterward and tested for bile acids. None were found. Four weeks later 1.5 gm. of sodium glycocholate in 12 cc. of water was injected into the left jugular vein of the same dog. In 31 hours 1,130 cc. of urine was collected. Bile pigment gave a marked reaction. No bile acids were found. Fourteen days later 1.3 gm. of sodium glycocholate in 9 cc. of water was injected in the right jugular vein of the same dog. Bile pigments were found, but no bile acids. Fourteen days later 2.2 gm. of sodium glycocholate in 14 cc. of water was injected intravenously into the same dog. The urine contained bile pigments, and there was a slight trace of bile acids.

² (167): "Aus diesen Versuchen geht deutlich hervor, dass durch eine Hemmung im Ausflusse der Galle der Pfortaderstrom um ein sehr Merkliches beeintrachtigt ist."

The conclusion that bile acids are the only toxic substances in bile was first reached by Röhrig in 1863. Filtered ox bile, 6 cc., was injected into the jugular vein of rabbits, resulting in death 2 minutes after the second injection. Following the injection of cholesterol, taurin, glycoll, and bile pigments separately, there was no reaction; and he deduced that the toxicity was in the conjugated bile acids. In the same year Landois supported Röhrig, by his findings in experiments with frogs, rabbits, and cats. An intracardiac injection of bile and bile acids was made; at first the heart beat more rapidly but later failed. The first graphic records were made by Traube in 1864. Using the kymograph, he showed that bile acids acted on the heart when given to a dog intravenously. The nervous symptoms in jaundice were attributed to nutritional disturbances as a result of anemia of the brain, caused by the destruction of the oxygen-carrying red cells in the blood.

Working with frogs and dogs, Leyden, in 1866, observed the toxic action of bile caused by various kinds of application, including intracardiac and intracarotid injections; and, finding bile acids in the blood of patients with icterus gravis, he concluded that bile salts have an "eminent" poisonous action.

After placing a frog's heart in bile, Schack, in 1868 observed the loss of irritability; and the morphology was so altered that the cross-striations of the muscle fibers disappeared.

Experimenting with dogs and guinea-pigs, Schiff, in 1870, made external biliary fistulas and found that the excreted bile quantity gradually sank to a low level and remained there. When all the collected bile was put into the intestine, the fistula output of bile increased to the previous normal. Dog bile or ox bile put into the stomach or small intestine caused a greater secretion of fistula bile. The injection of a larger quantity, 70-200 cc., produced a greater amount of secretion, which continued over a longer period; but the entire amount that went into the intestine was never quantitatively ac-

counted for. Injection into the blood had the same effect on the fistula-bile output. When the portal artery of cats was ligated, the circulation of the bile acids and pigment was more rapidly diminished. After a collateral circulation had been established, the bile substances appeared in the blood stream (general circulation) in larger quantities, because they were absorbed again from the intestine, instead of all being excreted. He concluded that bile was nontoxic, because in the enterohepatic circulation each time the bile made a circuit it grew smaller and smaller in amount. When the portal artery was obstructed, the absorbed substances went into the general circulation, causing toxic symptoms.

Freshly secreted bile was obtained from the hepatic duct of a rabbit and injected likewise into rabbits by Ranke in 1871, and no reaction followed; but the injection of 15 mg. of bile acids caused death. He concluded that there was no action on the heart but that the alkaline salts caused blood clots and thrombosis of the pulmonary arteries by breaking up the red cells.

Bile, bile salts, cholesterol, and other bile constituents were injected intravenously into dogs by Feltz and Ritter, 1874-76. When 15 cc. of beef or pig bile were injected into the crural vein of a dog weighing 15 lb., the heart became irregular, the respiration rate at first increased, then decreased, and the dog went into convulsions. Bile salts prepared from beef bile gave the same toxic symptoms. They concluded that the poisonous action of bile was in the salts: sodium taurocholate and sodium glycocholate. Intravenous injection of 0.46 gm. of sodium taurocholate per kilogram of body weight caused the death of dogs. An injection of 0.51 gm. of Platner's crystallized bile also caused death. They opposed the views of von Dusch, Röhrig, and Leyden and explained that sodium cholate and *Choloidinsaures*³ are not poisonous. They also showed that cholesterol in strong solution produced emboli but of itself is not toxic.

³ Old High German (Kühne [1034]).

It was observed by Bouchard, collaborating with Tapret, that a 2 per cent solution of bile salts in water killed a rabbit weighing 1 kg., but that the bile decolorized by carbon lost two-thirds of its toxicity. He concluded that bile salts were, indeed, less poisonous than the pigment but that they nevertheless destroyed parts of the cells in the body and thereby liberated the intracellular and imprisoned poisons. The elimination of these poisons through the kidneys caused injury, cholemia appeared, and then the disease progressed through acholia to uremia. He⁴ believed that as long as the kidneys acted in icterus the urine was poisonous and the bile non-poisonous, but that when the kidneys did not act the bile was poisonous and the urine nonpoisonous. In 1887 he reported that bile which had been filtered through animal charcoal, freeing it of the pigments, lost 60 per cent of its toxicity. He injected 4-6 cc. of beef bile intravenously into rabbits, causing the death of the rabbits. From these investigations he concluded that there are two poisons in bile: the biliary salts, which have been so recognized; and a substance which, up to his time, had not been appreciated from a toxic point of view, viz., the coloring matter. This he believed to be a new revelation in pathology. He surmised that the precipitation of the coloring matter and salts from the bile in the intestine prevented them from being absorbed, thus rendering the bile less toxic. The precipitated pigments and salts were, he thought, passed out of the body in the feces. He did not take into account the possibility of the animal charcoal removing some of the bile salts at the same time.

The present writer repeated these experiments and found that in the process of removing the bile pigments the specific gravity of the filtrate of bile was greatly reduced, and that the bile salts were reduced approximately one-half. The toxicity of bile was likewise reduced.

Bile in a dog's stomach caused no disturbance; but sub-

⁴ Bouchard (233, p. 780): "Ce liquide est extrêmement toxique; il l'est 9 fois plus que l'urine."

cutaneous injections in rats caused death if a sufficient quantity were used, according to Prevost and Binet, 1888. When a smaller quantity was used, a local abscess developed at the site of injection. An injection of 0.5 gm. of bile salts per kilogram of body weight caused the death of rabbits. In a second observation, they attributed death to the injections of 0.05 gm. of bilirubin per kilogram of body weight.

In 1889 de Bruin estimated that bilirubin was five times more toxic than the bile salts. He based his conclusions on intravenous injections of bile, and bile decolorized by animal charcoal, into rabbits. He found the latter much less toxic. In 1890 Plaesterer found that bilirubin, dissolved in sodium carbonate and injected subcutaneously or intravenously, always caused death. He used from 0.1 to 0.004 gm. of bilirubin from ox gallstones in frogs, rabbits, and mice.

The autopsy was significant in showing thrombosis of the intestinal vessels. Sodium carbonate itself in strong solution, when given intravenously, will cause *intra vitam* coagulation in the smaller vessels.

Determination of varying natural specific gravities of bile was made and recorded by Polimanti, 1896. He attempted to establish the relation of toxicity to specific gravity, and his experiments showed that bile toxicity does vary according to specific gravity. He used methods similar to those of Lugli.

The toxicity of filtered bile was investigated by Lugli, 1899, who stated that bile, decolorized by animal charcoal, was one-fourth as toxic for rabbits when given intravenously as that not decolorized. Fistula bile from dogs was injected into the large ear veins of rabbits. A portion of the same bile was also filtered and decolorized by animal charcoal until it was entirely clear and colorless. Injection of the bile was continued at a given rate until the animal died. It was necessary to use 83, 85, and 102 cc., respectively, to kill each of three rabbits. The rabbits weighed from 1 to 1.5 kg. The decolorized fistula bile was also injected, and required a somewhat greater quantity, namely, 136, 162, and 126 cc. for each of

EXPERIMENTAL HISTORY

three rabbits, respectively, following ligature of the vena porta. The average amount of dog fistula bile necessary to kill was 31.7 cc. per rabbit. When the same bile was decolorized, it was necessary to inject 119 cc., 175 cc., and 214 cc. From these experiments he concluded that "die entfärbte Galle ist viermal weniger giftig als die nicht entfärbte" and that, of the constituents of bile, bilirubin is the most toxic. He also concluded that bile was the most toxic secretion of the organism. Lugli found the toxicity of bile to be almost in direct proportion to its solid content and density. He believed that the poisons which go from the intestine to the liver were shut off by ligature of the portal vein, as shown in the accompanying tables. This work has been confirmed by Colasanti in 1899.

| | Density | Toxicity |
|--|---------|----------|
| Gallbladder bile. | 1,043 | 6.3 cc. |
| Fistula bile. | 1,018 | 21.5 |
| Fistula bile after ligature of portal vein. | 1,012 | 34.5 |

| | LIGATURE OF PORTAL VEIN | |
|------------------------------------|-------------------------|----------|
| | Before | After |
| Bile toxicity. | 21.5 cc. | 34.5 cc. |
| Coefficient of bile toxicity. | 0.281 | 0.161 |

Rabbit bile was used mainly by Meltzer and Salant, 1906, in their experiments; but ox, dog, and guinea-pig bile were also used. These various biles, boiled bile, and various bile constituents were injected mostly in the dorsal and ventral lymph sacs of frogs. From this work they arrived at the conclusions that the boiling of bile reduced the toxicity of the bile as a whole, while stagnant gallbladder bile became very toxic, the depressing element being the controlling factor.

This depressing substance caused coma, stupor, and paralysis. Bile also contained a tetanic element (exciting), causing convulsions, tetanic attacks, hyperesthesia, and excitation.

Bile salts were called protoplasmic poisons by Neufeld and Handel, 1908, and were found to have a cytotoxic effect, causing hemolysis of red cells, disintegration of white cells, disruption of spermatozoa, hemorrhage, albuminuria, and lysis of protozoa. Most of the previous investigators agreed that bile was toxic in some form or another. It was stated by Leyden that bile salts have the same toxicity and produce the same danger as bile pigment, while the other constituents are harmless.

The relative toxicity of bile from different animals may vary considerably. Rabbit bile, according to Bunting and Brown, 1911, is more toxic to rabbits than the bile of any other animal is to others of its kind or to rabbits. Gallbladder bile of the dog, when given intravenously to rabbits, has a much greater toxicity than fistula bile (Lugli). Fistula bile of dogs, given intravenously to guinea-pigs and rabbits, caused death. Gallbladder bile is three to four times more toxic than fistula bile. Fistula bile of various dogs differs; also, that of the same dog is different at different times, according to the variations in activity (?) and food intake. Bile salts in the blood are not in combination with the proteins, for the blood is not acid enough to cause this reaction (1491).

Intravenous injections of sodium taurocholate, 2 cc. of a 1:800 salt solution, in rabbits were used by Ponder, 1921; no evidence of hemoglobinuria or hemolysis in the serum was observed. By the Bertrand modification of the Pettenkofer test there was only a trace of bile salts in the urine. Details of this work will be given in the discussion of the effect of bile on the red cells.

Sodium glycocholate in 2 per cent (0.07 gm. per kilogram) solution given intravenously to rabbits had no marked action; 0.08 gm. caused restlessness; 0.09 gm. killed the animal; post-mortem intestinal peristalsis was increased. An injec-

tion of 0.08 gm. of sodium taurocholate caused tonic convulsions and slow breathing. Gillert thought that the toxicity of the different bile acids varied according to the inverse proportion of their surface tensions.

Mucin in the bile delayed absorption and prevented hemolysis of the red blood cells, Mellanby (1262). When mucin-free bile or bile salts were injected into the gut, they frequently caused hemolysis of the red cells and hemoglobinuria, which suggested a possible function for mucin in the bile. Bile is much less active as a pancreatic juice excitant than mucin-free bile.

The loss of bile by external fistula, according to Düttmann, 1927, caused acidosis, with altering of the calcium metabolism, owing to inability to absorb vitamins A and D, which are contained in the fat, as bile salts are necessary for the absorption of fat from the intestine. The absence of the vitamins is followed by mobilization of the calcium from the bone, causing osteoporosis. Discussion will follow under the subject of "Bile Fistula."

Bile acids and bile pigments were precipitated in the livers of rabbits by treating the livers with a 3 per cent solution of barium chloride (Forsgren, 1928). The microscopic examination of the cells of the liver stained by acidified fuchsin, according to Mallory's method, showed a large amount of "secretion granules" which Forsgren believed to be bile acids. More granules were seen following the feeding of bile than after an ordinary dietary regime. These granules in some pre-excretory form actually lay within the liver cells. He concluded that the liver cells may hold a variable quantity of specific bile constituents. This quantity sometimes occurs sparingly and at other times more abundantly.

DISCUSSION

These variations in the toxicity of different biles may be explained in various ways: (1) The quantity of bile acids in the bile may vary considerably. (2) The kind of bile acids in

the bile may vary, such as taurocholic acid in dog bile and glycocholic acid in ox bile. (3) The amount of protective substances, such as cholesterol and protein, may vary substantially, the smaller the amount of cholesterol present with bile acids remaining the same, the greater the toxicity. (4) Specific proteins or other constituents may cause reactions.

The toxicity of sodium taurocholate and sodium glycocholate is not theoretically comparable at the present time, as the former has never been isolated in absolutely pure form;⁵ when a high degree of purity is obtained, there is a sudden breaking-up of sodium taurocholate into taurin and cholic acid, and a gummy mass is formed instead of crystals.

⁵ Taurocholic acid has recently been synthesized, but no experimental evidence is available as to toxicity.

CHAPTER III

METHODS OF INVESTIGATION

IN JAUNDICE, presumably, bile slowly accumulates in the tissues. When large quantities of bile constituents are injected into the blood stream, they act suddenly and are rapidly removed by the normal liver. This is best seen in bile fistula dogs, where bile or bile salts are given by mouth or intravenously. The output is increased in proportion to the amount given.

The first method (Deidier in 1722) used was that of intravenous injection of bile in which bile was taken from a human body at necropsy and injected into a dog. The next method (Saunders in 1795) was that of ligation of the common duct. The symptoms of jaundice which appeared in experimental animals were presumed to be similar to those of jaundice in a human. Since the bile was prevented from entering the intestine, the experimenters concluded that bile was a poisonous substance and caused icterus. Later, bile from various sources, such as fistula and gallbladder bile, was obtained and injected into different animals intravenously, subcutaneously, intraperitoneally, in the dorsal lymph sac of frogs, and intra-arterially.

The intravenous method is criticized by some investigators because bile may cause emboli and because it acts quickly on the heart, and also because large quantities are suddenly and rapidly introduced. The intraperitoneal and subcutaneous injections may cause local necrotic products, which may be absorbed, causing toxic symptoms and thus interfering with the interpretation. Extensive necrosis following subcutaneous injections of bile was observed. The action of bile is frequently retarded or inhibited by exudates. Bile introduced

into the dorsal lymph sac is absorbed fairly rapidly, but the experimental use of the method is limited to the frog.

The method of testing the action of bile on tissues or organs by the application of bile directly to the tissues is certainly not similar to the action of bile in the presence of jaundice. Bile in jaundice does not come in direct contact with the pericardium; it reaches the heart through the blood vessels. Also, bile ordinarily does not come in contact with the serosa of the intestine, as in the gut-strip method of testing; it comes in contact with the mucosa. The bile of one species of animal may be so different from that of another that, when used in a different species, it may cause entirely different symptoms or none at all. Therefore, in order to determine the toxicity of bile in the different animals, it would be necessary to investigate a very large number of animals. In the Eck fistula dogs, it is difficult to conclude that when bile is reabsorbed the toxic symptoms can be attributed to bile, as many other factors are involved.

Bile salts were applied to the tracheal mucosa of the rabbit by Wasbutzky, in 1879, causing an immediate reaction on the heart, respiration, and central nervous system.

Methods of investigation which simulate as nearly as possible the conditions, normal and pathologic, found in the human are quite necessary. When these are developed and carefully controlled, and chemically pure substances are used, we may be able to discover facts. Indirect, inadequate, faulty, and pseudoscientific work almost obscure the entire horizon in this field.

CHAPTER IV

CONSTITUENTS OF BILE

COMPLEXITY

THE complexity of bile has been known only within the past century. Hippocrates¹ and Galen² recognized many variations in the physical characteristics of bile and, on that basis, sought to explain the cause of all diseases and variations in temperament. Cholesterol was the first constituent to be identified (Conradi in 1775), and with the advance in chemistry other constituents were discovered. Faithhorn, in 1822, presented the following chemical analysis of bile:

- I. A large proportion of water.
 - II. A substance closely resembling albumen.
 - III. A peculiar resinous inflammable matter naturally and intimately mixed with it.
 - IV. Soda, forming a soap or saponaceous extract.
 - V. Some neutral salts.
 - VI. And a small quantity of oxide of iron besides a small quantity of odorant.
- [and] Some chemists have thought they could detect saccharine, but this is not conclusive.

He adds that in a "person under the influence of a depressing passion . . . the bile easily coagulates . . . thus gallstones are formed." However, it was not until the middle of the nineteenth century that identification of many of the constituents was made. In rapid succession appear the great names of Fourcroy and Vauquelin, 1790; Gmelin, 1826; Demarçay, 1838; Berzelius, 1840; Pettenkofer, 1844; and von Gorup-Besanez, 1846—all working on the identification of bile constituents. With the discovery of the bile acids by

¹ Hippocrates, 468-367 B.C.

² Galen, A.D. 130-200.

Strecker, 1848, more intense chemical work followed, by such eminent chemists as Marsson, 1849; Hoppe-Seyler, 1862; Hammarsten, 1881; and finally Wieland, who was given the Nobel Prize in 1927 for his distinctive work on the chemistry of bile acids. Heinrich Wieland and his co-workers have done an extensive amount of work on the chemistry of bile, the constituents, especially the salts and their variations, and modifications *in vivo* and *in vitro*. During this period of development, various systems of nomenclature have been used; there is still little conformity of terminology in the various languages.

The number of identified constituents in bile is continuing to increase, and the field ever widens. The work, however, is seriously hampered by the lack of a specific test for the main building-stone of bile acids, cholic acid. Some variations of bile constituents under normal conditions have been pointed out by Bidder and Schmidt, 1852; Stadelmann, 1891; Whipple and Hooper, 1913; and Rous, 1920. A large number of factors cause these variations in volume, character, and constituents, the most common of which are diet, climate, exercise (?), and time of day.

Pathologic variations in bile have been observed during the course of such diseases as infections and poisonings, cirrhosis of the liver, and pneumonia, and following chloroform anesthesia. Many poisons—for example, arsenic and phosphorus—are excreted in the bile and affect not only the liver but also the bile. While many variations in bile have been observed in man, most of the experimental work has been done on dogs with external biliary fistula of various types. The objections to the conclusions drawn from work on biliary fistula are based mainly on the fact that, sooner or later, infection invades the bile passages and liver, creating an abnormal condition. Consideration must also be given to the fact that in fistula the expulsion of bile is continuous, while in the animal with a gallbladder the ejection is intermittent.

The excretion of bile salts varies considerably according to

conditions. When bile salts are fed, a large portion is soon excreted in the bile. In an animal with complete external biliary fistula, the bile-salt excretion decreases to a low level, but some is always produced. The bilirubin content normally varies somewhat, but mainly in proportion to the concentration of the bile; but the total daily output seems to be fairly constant. In hemolytic jaundice there is a definite increase. Cholesterol excretion varies normally; but in disease or following sterol feeding, there are marked variations of the amount in the bile. Some of the bile constituents vary with their concentration in the blood, just as urea varies. With an excessive bile secretion there is usually a slight increase in the total output of urea in the bile.

CHARACTERISTICS

Bile has a protean character.

COLOR

Bile assumes different appearances. In man the biliary fistula bile is usually a light orange-yellow and the gallbladder bile is a deeper orange-brown. The color normally differs according to the pigment concentration and the type of pigment present. Bilirubin gives an orange color; biliverdin, a greenish color. The color of bile is not the same in all animals: it is colorless in the guinea-pig, orange-yellow in man and dog, greenish in the ox, deep green in the lion (Tanaka), and an intense green in birds. On standing, oxidation of the pigments takes place, causing a change in color from orange to green, to blue, and then to brown. The reddish color in bile is usually caused by hemoglobin. Black bile occurs in typhus and cholera. Dyes and drugs may modify the color of bile. These are listed later in this chapter.

QUANTITY AND CONCENTRATION

The daily quantity of bile secreted by man is extremely variable. It is impossible to establish the exact amount in man or other animals under normal conditions. Thus, quan-

titative determinations of bile volume and solids by the fistula method are not accurate, owing to the loss of fluid and solids, causing an abnormal metabolism of the liver. The fistula method is probably the best at the present time. Here, again, difficulty arises because of the absence of the influence of the normally reabsorbed bile. Cholagogues cause an increased output of bile salts, both relative and absolute. The enterohepatic circulation of the biliary secretion products causes stimulating bile constituents, such as bile salts, to be repeatedly brought into play. Stadelmann, 1891, found that two-thirds of the bile salts were reabsorbed from the intestine.

The volume of bile secreted is somewhat variable, depending on the type of food intake, a meat meal causing a greater secretion than a carbohydrate meal (Voit). The hepatic bile secretion is fairly continuous, but the expulsion of bile into the intestine is intermittent. The volume diminished following an abdominal operation on a dog, and it required 10 days for the bile to take on its normal character (McMaster, Broun, and Rous). Cholagogues, like bile salts, increase the volume; and anticholagogues, like atropine, decrease it. An increase from 14° to 24° C. of the temperature of water given the dog caused a 25 per cent increase in the volume output of bile (Brugsch and Horsters [277]).

Human bile output from biliary fistula averages 300-700 cc. in 24 hours. Pfaffe and Balch reported a case with secretion of 525 cc.; Robson, 940 cc.; Bidder and Schmidt found an output of 13-29 cc. per day per kilogram of body weight in the dog; 14.5 cc. in the cat; 25.4 cc. in the sheep; 136.8 cc. in the rabbit; and 175.8 cc. in the guinea-pig. Horrall found an average daily secretion of 1,000 cc. of bile containing 21 gm. of solids in a man having a biliary fistula with obstruction of the common duct caused by carcinoma. The dried substance in fistula bile is 1-4 per cent; in gallbladder bile 20 per cent (Brand); in fistula bile 1.6-3.5 and in gallbladder bile 16-17 per cent (Hammarsten). The gallbladder bile is eight to ten times more concentrated than the hepatic bile (Hammarsten).

CONSTITUENTS OF BILE

SPECIFIC GRAVITY

The specific gravity of human bile varies from 1.008 for fistula bile (Copeman and Winston) to 1.040 for gallbladder bile (Frerichs), and for ox gall from 1.016 to 1.037 (Marshall). The density of canicular bile is from 1.009 to 1.011. The quantity of fluid intake causes little change in density, either directly or indirectly (Dolore).

The freezing-point is about -0.56°C . to -0.61°C .

REACTION—pH

The reaction of bile varies considerably according to its location, as shown by Rous (1633), using vital staining in the dog (see the accompanying tables). A low pH 4.0 of gall-

CANICULAR LIVER BILE

| Dye | Color | Reaction |
|------------------|--------|---------------------|
| Thymol blue..... | Yellow | pH less than 8.4 |
| Cresol red..... | Red | pH greater than 7.4 |
| Phenol red..... | Red | pH greater than 7.4 |

CANICULAR GALLBLADDER BILE

| Source | Dye | Color | Reaction |
|------------------------|--------------------|--------|--------------|
| In center of bile..... | Bron cresol purple | Purple | pH 6.4 |
| Near mucosa..... | Bron cresol purple | Yellow | pH below 5.4 |

bladder bile was found by Laverigne. Also there is considerable variation in the reaction of bile of laboratory animals, as the table herewith shows.

| Kind of Bile | Source | Reaction |
|-------------------------|-----------------------|---------------------------------|
| Guinea-pig..... | Gallbladder normal | 7.5 |
| Rabbit..... | | 7.08-8.42 (Usuki) |
| Dog..... | | To the alkaline side (Tuzioka) |
| Ox, sheep, and dog..... | | 7.0-7.5-8.4 (Neilson and Meyer) |

Human bile varies from 5.70 to 7.86, according to the conditions and location at the time of testing; hydrops of the gallbladder bile, 5.77; fistula bile, 7.3; gallbladder bile, 5.72–7.85 (Tschopp); fistula bile, 8.0–8.6; gallbladder bile, 7.7–8.6 (Neilson and Meyer). Hepatic-duct bile is alkaline to litmus 7.4, changing on exposure to 9.2 (Neilson and Meyer). The pH of bile on the capillary side of the liver cells tends more to the alkaline (Petow and Wittkower); liver cells, 6.5–7.0; bile, 7.0; Kupffer's cells, 5.0, which are much more acid than the parenchymal cells; blood capillary, 7.3–7.4.

Variations in reaction are caused by diet, meat causing an increased acidity, vegetables an increased alkalinity. Duodenal bile of fasting dogs ranges from 4.68 to 7.83 and lean-meat feeding causes a decrease of the pH from 7.00 to 3.00, while loss of bile does not significantly alter the pH of the duodenal contents (McRoberts). Bacteria causes an increased acidity (Bonner). Histamine increases the alkali reserve in the bile, while adrenalin and insulin cause a decrease (Karatygin and Hefter). Bile salts by mouth increase the pH of bile in Thiry-Vella fistula animals (Kuramoto). Sodium bicarbonate given intravenously or orally has no effect on the pH of Rous fistula bile (Ottenberg). Standing causes a low H-ion concentration (Neilson and Meyer). Atophan causes an alkali increase even to a pH of 8.3 (Rosenthal).

PHYSICAL AND CHEMICAL REACTIONS

The surface tension of taurocholic acid decreases in proportion to the amount of HCl added and increases with the NaOH (Iota). The different salts of taurocholic acid, such as Na, Ca, and Cu, have different surface-tension values (Shiono).

Bile acids have specific optical properties. The rotary dispersion also depends on the different salts of the bile acids. Cholic, desoxycholic, glycocholic, and taurocholic acids have been determined (Josephson).

The colloidal osmotic pressure of the bile depends on the

resorption of chloride by the gallbladder, the liver bile increasing from two to four times in the gallbladder. The colloid-osmotic pressure changes from 0 to 1,400 mm. H_2O during the thickening concentration of the bile in the gallbladder (Frey). The electrical resistance of laminaria in sea water has been determined; sodium taurocholate causes a decrease in permeability, which is opposite to the action of sodium chloride; this is modifiable according to the concentration of the bile salt (Osterhout). The protein osmotic pressure of liver bile is less than that of gallbladder bile but three times higher than that of the blood. The water and chloride content of the gallbladder bile are inversely related to the protein osmotic pressure (Frey).

The osmotic pressure is slightly greater than that of the blood.

The dissociation constant of glycocholic acid is 4.0×10^{-5} (Hammarsten); for taurocholic acid the pK is 1.17-1.39, and for glycocholic acid 4.40 (Josephson).

COMPOSITION

GENERAL ANALYSIS

The chemical composition of human bile has been determined with bile taken from the gallbladder soon after accidental death, at operation, and at autopsy after natural death. Fistula bile from man has been analyzed repeatedly. The accompanying table shows the findings by various investigators.

Neutral fats and lecithin are absent in the gallbladder bile of the ox, hog, and dog, or are present in very minute quantities, according to Jones and Sherberg, who used the acrolein method of testing for fats. Heteroalbuminocholia was determined by Matsuda by the precipitin reaction. A liver injury caused by drugs, such as arsenic, phosphorus, and chloroform, and a mechanical injury, such as an incision in the

liver, permit protein to pass into the bile. But when Kupffer's stellate cells are saturated with India ink, no protein can pass into the bile. Mucin in the bile varies both physiologically and pathologically: increased by infection, normal 0.2–0.7 gm. per 1,000 cc. in the dog, 0.8–2.8 gm. in man; with obstruction of the common duct, increases to 6.37 gm. after 24 hours (Mallet-Guy). Mucinocholia and albuminocholia be-

COMPOSITION OF HUMAN BILE

(Parts per 1,000)

| | Hammarsten (755) Liver Bile | Frerichs (632) Gallbladder | Von Gorup- Besanez (2013) Gallbladder | Yeo and Herroun (2158) Fistula | Mayo-Robson (1585) Fistula |
|------------------------------------|-----------------------------------|-------------------------------|--|---|----------------------------------|
| Solids..... | 25.40 | 140.0 | 101.9 | 12.84 | 18.02 |
| Water..... | 974.60 | 860.0 | 898.1 | 987.16 | 981.98 |
| Mucin* and pigments. | 5.15 | 26.6 | 14.5 | 1.48 | 1.30 |
| Bile salts..... | 9.04 | 70.2 | 56.5 | 2.20 | |
| Taurocholate..... | 2.18 | | | 0.55 | 0.09 |
| Glycocholate..... | 6.86 | | | 1.65 | 7.51 |
| Fatty acids and soap.. | 1.01 | | | | 0.97 |
| Cholesterol..... | 1.50 | 1.6 | | | 0.45 |
| Lecithin (phospho- lipids)..... | 0.65 | | 30.9 | 0.38 | |
| Fat..... | 0.61 | 3.2 | | | 0.12 |
| Soluble salts..... | 7.25 | | 6.3 | 8.78 | 7.58 |
| Insoluble salts..... | 0.21 | | | | |

* True mucin has been found in human bile.

come more marked in hepatic disorders (Da-Rin and Bacchetta).

Normal human bile contains, in the form of bile salts, mainly sodium glycocholate, sodium taurocholate, sodium cholate, sodium choleate, and some sodium desoxycholate. Other bile salts may be present but in minute traces. The normal human fistula bile contains bile acids in the amount of 2,000 mg. for each 100 cc. of bile, as determined by Gray and McGowan, using the Gregory and Pascoe method.

The daily output of bile salts by man is about 6 gm. (Herzfeld and Haemmerli). The bile-salt output by bile fis-

tula dogs for 10 hours is from 1 to 1.5 gm. (Chabrol and Benard, Wislicki). The quantity of bile salts depends on a number of variables, which will be discussed later.

Cholesterol, lecithin, palmatin, stearin, olein, and mucin occur in the normal bile. Lactic acid, 4 mg. per 100 cc., is found in the bile of normal rabbits. It increases in proportion to the lactic-acid content of the blood (Mizuno).

Hoppe-Seyler lists the following as normal constituents of bile: bile salts, bile pigment, cholesterol, mucin, ethereal sulphates (human and shark bile), conjugated glycuronic acids, fats, soaps, urea, jercorin and other phosphates, lecithin, hydrochloric acid, phosphoric acid, and sulphuric acid salts such as Na, P, Mg, Fe, and Cu.

HORMONES

Oestrous hormone was found by Gsell-Busse (734) in the bile of woman. Purified bile salts contained none, and commercial bile salts contained very little. This is the only hormone found, as yet, in bile.

ENZYMES

Considerable work has been done on enzymes in bile. There is some evidence of traces of amylase, but very little evidence of lipolytic and proteolytic enzymes. Phosphatase has been observed. These enzymes appear in various body fluids and are probably present in the bile, either due to pathologic hepatic cells or to an overflow from the blood. However, pancreatic enzyme was found by Popper in 37 of 219 cases of man coming to operation. Of 20 patients with pancreatic juice in the bile passages, none had pancreatic disease, 17 had gallstones.

VITAMINS

An attempt was made by Miss Cooper (382) to determine the vitamin content of bile; but because of the great toxicity of bile when used in the feeding experiments, the work was discontinued. Using pigeons and guinea-pigs, Makimura (1170) claims to have shown not only that the vitamins A, B,

C, and D are in bile but that they are absorbed by the small and large intestines and that there is an enterohepatic circulation which conserves the vitamins. Guinea-pigs with rickets, fed fresh bile, returned to normal, indicating that vitamin D is present in bile. Ergosterin and other sterins have been isolated from ox gall and dog fistula bile (Syderhelm). Since cholic acid, methyl ester, and desoxycholic acid exposed to ultraviolet light are antirachitic (Uraki), there seems to be a chemical relation between vitamins and bile acids. The intermediate form between ergosterin and bile acid is trioxystercholeonic acid isolated from winter bile of the frog by Shimizu.

Pucher and Sly (1916) investigated the gallbladder bile taken at operation, fistula bile, and gallbladder bile taken at autopsy and found that urea, uric acid, creatinine, amino acids, nonprotein nitrogen, and sugar appear in concentrations comparable to those in the blood serum.

Gallbladder bile obtained at necropsy contains constituents somewhat different in value from gallbladder bile obtained at operations and from fistula bile. Since there is a profound change in the blood just before death, one would also expect a change in the bile. It cannot be said definitely that these substances are found in normal human bile, as presumably the diseased condition that causes operation or death may have some effect on the constituents of the blood and the bile.

SUGAR

Glycocholia was observed by Claude Bernard in pancreatic diabetes in the dog. A reducing substance was found in the fistula bile of 63 dogs by Baltaceano and Vasiliu which is identical with the glucose of the blood. They found sugar in two forms: free sugar and protein sugar. There is a relation between glycemia and sugar in the bile. The sugar in the gallbladder is a very concentrated protein sugar, ten to fifteen times more concentrated than in duct bile and three to five times more concentrated than in the blood. These reducing

CONSTITUENTS OF BILE

substances in the bile were increased by carbohydrate feeding, decreased by insulin, increased by adrenalin, and altered slightly by meat and fat feeding, according to Aszodi. He concluded that the reducing substances found in normal bile were similar to blood sugar, with slight differences. These investigations were made on bile obtained from the gallbladders of dogs. The bladder had previously been attached to the abdominal wall so that a needle could be introduced through the abdominal and gallbladder walls into the bladder cavity.

MINERALS

The mineral salts in human bile in part pass through the liver, and the rest pass through the wall of the finer bile ducts from the portal vein (see the accompanying table).

| | MINERAL SALTS—HUMAN | |
|---|--|--|
| | Gallbladder (Frerichs) (Parts per 1,000) | Fistula (Jacobsen) (Parts per 1,000) |
| KCl..... | | 0.28 |
| NaCl..... | 2.5 | 5.4 |
| Na ₂ PO ₄ | 2 | 1.3 |
| Ca ₃ (PO ₄) ₂ | | 0.37 |
| MgP ₂ O ₇ | 1.8 | Trace |
| CaSO ₄ | 0.2 | |
| NaCO ₃ | | 0 95 |

The following metals have been found in bile: copper (Bernard), lead (Annuschat), iron (Bouchard), mercury (Autenrieth), antimony, tin (Lussana), zinc, aluminum (Müller), cadmium (Marmé), cobalt (Canjolle), bismuth (Brich), iodine (Bernard), lithium, and phosphorus. These minerals usually occur in the form of sodium or potassium salts. Iodine is excreted in the bile, according to Elmer and Luczynski, who found in the bile of fasting rabbits, 4–14 y per 100 cc., and after feeding, 69–82 y per 100 cc. Maurer and Ducre found in rabbit bile, 15–62 mg. per 100; Pfeifer in beef bile, 1.5–1.8 mg. per 100; and Fieser in dog

bile, 13-113 mg. per 100. Elmer and Luczynski have concluded that the liver has a definite role in the metabolism of iodine. In dogs with biliary fistula the iodine elimination in the bile is greatly increased by the use of thyroxin (Barnes).

Bromine and iodine have not been found in the bile of normal rabbits (Maruno). Organic compounds are more easily excreted than inorganic, and there is greater excretion when given intravenously than orally. Iodine, bromine, and chlorine are excreted by way of the parenchymatous cells, as

MINERAL SALTS IN BILE, HOPPE-SEYLER (845)

Parts per 1,000

| | Dog Gallbladder | Dog Fistula | Human Fistula (Yeo and Herroun) |
|---|-----------------|-------------|---------------------------------------|
| NaCl..... | 0.015 | 0.185 | 0.7168 |
| K ₂ SO ₄ | .004 | .022 | |
| Na ₂ SO ₄ | .050 | .046 | .045 |
| Na ₂ PO ₄ | | | .015 |
| Ca ₃ (PO ₄) ₂ | .080 | .039 | .003 |
| Mg ₂ P ₂ O ₇ | | | |
| Fe ₂ PO ₄ | .017 | .021 | |
| NaCO ₃ | .005 | .056 | .051 |
| CaCO ₃ | .019 | .030 | 0.0100 |
| MgO..... | 0.009 | 0.009 | |
| Total..... | 0.199 | 0.408 | |

Cu, trace habitually present (copper sulphate [Cl. Bernard]).

Fe, trace, variable (Bouchard).

Zinc, trace often.

Silica, trace often.

shown by the diminished excretion following liver injury by phosphorus and by the absence of change following the use of India ink.

Iron and copper are constant in the bile of man obtained from the gallbladder at operation or by fistula; the iron content is 0.031-1.68 mg. per cent, copper, 0.063-1.07 per cent. In bile obtained from dogs and guinea-pigs the iron is 0.09-0.18 per cent (Judd and Dry).

The mineral content of the bile is roughly proportional to the mineral intake in food (see table above).

The sodium, potassium, calcium, and manganese salts of dehydrocholic acid have been injected also into rabbits with gallbladder fistulas. The same bile acid salts were excreted in the bile (Neubauer).

PIGMENTS

The principal pigment in bile is bilirubin. It gives a golden-yellow color to the hepatic bile. The bilirubin content of human bile has been estimated at from 0.5 gm. per day (Eppinger) to 2.1 gm. per day (Patou). In biliary fistula in human bile the output of bilirubin is 5-7 mg. per kilogram of body weight (Eppinger), in dog's bile, 0.6-0.7 mg. (Stadelmann). In normal gallbladder bile removed from the cadaver the concentration of bilirubin is from 0.05 to 0.125 gm. per cent, and in very concentrated bile 0.4 gm. per cent (Lepehne). An oxidation product is biliverdin (Heintz in 1851), which is found in the gallbladder bile of man but more commonly in that of Herbivora and cold-blooded animals. Bilirubin and biliverdin are found in gallstones. Biliverdin and biliprasin have been observed in a human six-month embryo (Florentin). Other oxidation or reduction products of bilirubin are hydrobilirubin (Maly), bilifuscin (Städeler), biliprasin (Städeler), bilihumin (Städeler), bilicyanin (choletin? cholecyanin?) (Hensius, Campbell). Bilifuscin has been isolated and analyzed from gallstones (Weinberger); also choleprasin (Küster). In the bile of musk ox and hippopotamus is cholehematin (MacMunn) or bilipurpurin (according to Loebisch and Fischler), which is not a bile-pigment derivative but comes from chlorophyll (Fisher). This same pigment was obtained from sheep bile (Marchlewski) and from dogs fed chlorophyll-containing plants (Broun, McMaster and Rous). Reduction products of bilirubin are urobilin and urobilinogen, which are absorbed from the intestine.

Hemoglobinicholia has been observed by Muir and Heggie in rabbits, following toxic conditions with liver change, such

as are caused by phosphorus, phenylhydrazine HCl, saponin, and analine.

The porphyrins are also absorption products from the intestine and are rarely found in normal bile. They occur in the form of copraporphyrin and uroporphyrin. In sulphanol poisoning hematoporphyrin is excreted in the bile in large quantities (Neubauer). However, van den Bergh found that the protoporphyrin from the red blood cells is excreted in the bile as koproporphyrin. Weiss had a patient with a porphyrin gallstone. Carotin is also found in the bile, but rarely. These pigments will be dealt with in greater detail in the section on bilirubin.

VARIATIONS IN NORMAL BILE

The bile of land animals usually contains the bile salts in combination with sodium; the bile of water animals, the potassium salts. Taurocholate usually predominates in the bile of carnivorous animals, and glycocholate in the herbivores. The bile of most animals contains cholic acid, in some only traces and in others a large proportion. In the following list of the peculiarities of the various biles, the bile

| | |
|-------------|--|
| Rabbit..... | Desoxycholic acid (Okamura; first by Mylius in 1882) |
| | Cholic acid |
| | α -lago-desoxycholic acid (Kishi) |
| | β -lago-desoxycholic acid (Kishi) |
| | Lithocholic acid (Kishi) |
| Man..... | Oxalic acid (Larvonat) |
| | Desoxycholic acid (Wieland in 1924) |
| | Anthropodesoxycholic acid (Wieland in 1924) |
| | Lithocholic acid (Wieland) |
| | Choleic acid (Wieland) |
| | Chenodesoxycholic acid (Wieland) |
| | Cholalic acid (Schöppen) |
| | Fellic acid (Schöppen) |
| | Cholic acid |
| | Taurochenodesoxycholic acid (Wieland in 1924) |
| | Glycodesoxycholic acid (Hammarsten) |

| | |
|--------------------|---|
| New-born baby..... | Urea—much (Schutzenberger) |
| | { Musty smell in methemoglobin (?) (Wertheimer and Myers) |
| | Taurocholic acid—only (Hammarsten) |
| | Taurocholeic acid (Wahlgren) |
| | Glycocholic acid—trace (Wahlgren, Stadelmann) |
| Dog..... | Glycholeic acid (Stadelmann) |
| | Allantoin |
| | Creatine |
| | Creatinine |
| | Amino acids |
| | Ammonia |
| | { (Yashimuri) |
| | { Sterocholic acid (Wieland) |
| | Choline-neurine (Strecker) |
| | Propionic acid (Dogiel) |
| | Acetic acid (Dogiel) |
| | Lithocholic acid (Fischer in 1911) |
| | Choleic acid—small amounts (Latschinoff) |
| | Myristic acid (Lassar-Cohn) |
| | Cholic acid (Lassar-Cohn) |
| Ox..... | Nucleoalbumin (Hammarsten) |
| | Carotin-like (Fische and Rose) |
| | Chlorophyll (Verne) |
| | Urea (Popp) |
| | Glycholeic acid (Wahlgren) |
| | Taurocholeic acid (Wahlgren) |
| | Taurodesoxycholic acid (Hammarsten) |
| | Anthropodesoxycholic acid (Wieland) |
| | Sapocholeic acid (Wieland and Hanke) |
| Musk ox..... | { Glycodesoxycholic acid (Hammarsten) |
| | { Cholic acid (Hammarsten) |
| Sheep..... | { Cholehematin |
| | { Phylloerythrin (McMaster) |
| | { Taurocholic acid (Yamasaki) |
| | Tauroisolithocholic acid (Hosizima) |
| Fowl..... | { Gallodesoxycholic acid (Windaus) |
| | Chenodesoxycholic acid (Windaus) |
| | Taurochenodesoxycholic acid (Yonemura) |

| | |
|---------------------------------------|---|
| Goose..... | { Chenotaurocholic acid (Marsson, Heintz) Chenocholic acid (Marsson) Gallodesoxycholic acid (Windaus) Taurochenodesoxycholic acid (Windaus in 1924) Chenodesoxycholic acid (Windaus) |
| Fish..... | { Taurocholic acid—only (Hammarsten) Tetrodotoxin (Tahara) Potassium, instead of sodium, bile salts |
| Mullet..... | Taurochenodesoxycholic acid (Wanatabe) |
| Shark and ray..... | { Chenotaurocholic acid—third form (Hammarsten) α - and β -scymnol sulphuric acid—gives typical bile acid reactions (Hammarsten in 1898) Diastatic enzyme (Jacobsen) |
| Turtle..... | Tetrahydroxysterocholanic acid (Yamasaki) |
| Fish (<i>Serola quinqueradiata</i>) | Cholic acid (Ikoma) |
| Ray..... | Urea—chief constituent (Hammarsten) |
| Cod..... | Potassium taurocholate (Strecker) |
| Fish otter..... | Nutriadesoxycholic acid (Bright and Benedict) |
| Fresh-water fish..... | Glycocholic acid (Strecker) |
| Mollusk Gastropod Crustacean | { Cholerubin (Krunkenberg) |
| Walrus..... | Phocataurocholic acid (Hammarsten) |
| Seal..... | α - and β -phocochocholic acid (Hammarsten) |
| Winter frog..... | Trioxysterocholenic acid (Shimuriza) |
| Toad (<i>Bufo</i>)..... | { Bufodesoxycholic acid (Okamura) Trihydroxysterocholenic acid (Shimizu) |
| Snake (<i>Python tigris</i>)..... | Sodium taurocholate—the only bile acid in snake (Iwato) |
| Polar bear..... | Ursodesoxycholic acid (Hammarsten) |
| Bear..... | Ursodesoxycholic acid (Shoda) |

| | |
|----------------------|--|
| | { Hyodesoxycholic acid (Windaus in 1923) |
| | { Hyocholalic acid (Strecker and Gunderlach) |
| | { Hyocholic acid (Gunderlach) |
| | { Hyoglycocholic acid (Gunderlach) |
| Pig..... | { Hyotaurocholic acid |
| | { Also another glycocholic acid (Jobin) |
| | { Cholin (neurin?) (Strecker) |
| | { Urea (Popp) |
| | { 3-hydroxy-6-keto-allocholanic acid (Fernholtz) |
| Herbivora..... | { Choloheatin (McMaster) |
| | { Phylloerythrin |
| Peruvian guano..... | { Guanocholic acid (Hoppe-Seyler) |
| Oriental bezoar..... | { Lithofellic acid |
| | { Lithobilic acid |
| | { Litholitic acid |
| Lion..... | { Taurocholic acid (Tanaka) |
| Cat..... | { Taurocholic acid (Iwato) |

acids, pigments, and some of the other predominate substances are given. A quantitative analysis of most of these substances has not been made; so only a qualitative listing has been attempted (see p. 33).

Cholic acid comprised 50 per cent of the total bile acids, according to Doubilet and Colp, in fistula bile obtained from 27 patients with common duct obstruction; while cholic acid composed only one-sixth of the total bile acids in patients with inflammation of the ducts.

PATHOLOGIC BILE

DISEASE

In disease the metabolism of the human body is modified, substances are elaborated and new substances formed, or there is a quantitative variation of the normal substances. Any of the following may be eliminated in bile:

Acetone.....In coma

Albumin..... { In phosphorus and chloroform poisoning (Matsuda)
 { In Bright's disease and cardiacs with enlarged liver

| | |
|------------------------------|---|
| Fibrinogen..... | In phosphorus poisoning (Lang) |
| Glucose..... | In diabetes mellitus |
| Hemoglobin..... | Following transfusion, intoxications, poisoning with aniline and toluidine |
| Leucine } Tyrosine } |In icterus gravis (Fürth) |
| Proteins, various kinds } | In pneumonia |
| Urea..... | In uremia |
| Uric acid..... | In hepatic cirrhosis (Fortunato) |

Amino acids were found by Takaki in the bile of a child having acute yellow atrophy of the liver and a spontaneous common-duct fistula. He isolated, from 1,500 cc. of bile: arginine, 0.18 gm. as picrate; lysine, 0.06 gm. as picrate; tyrosine, 0.03 gm.; and leucine, 0.43 gm. In fresh human bile Müller found 100 mg. per cent of lysine, tyrosine, arginine, histidine, and free choline.

From bile obtained from dogs with biliary fistula the following have been isolated by Yoshimura: allantoin, 573 mg.; creatine, creatinine, 2.7 mg.; amino acids, 5.5 mg.; ammonia, 5.7 mg.; by Hammarsten, urea; and by Brugsch and Rother, uric acid. Urea is found in duodenal bile in both normal and diseased liver; the normal is 2 mg. per cent, which is increased by diseased gallbladder and liver (Lucke).

Indican is present in normal bile at 0.06–0.12 mg. per cent, approximately the same as in the blood (Inoue), which is 3–6 per cent of the output in urine. In ileus the indican in bile is increased to 13–20 per cent of the output in the urine. The liver and kidneys act as compensatory organisms for the output of the end-products of metabolism. They also serve, according to Faludi, to compensate each other under pathologic conditions.

DRUGS

In cases of poisoning with minerals and drugs, the liver eliminates some of them in the bile. Bile salts readily combine with many inorganic poisons and many more organic

poisons (alkaloids), such as strychnine, brucine, and quinine, rendering them less toxic. These may be eliminated in the bile by the liver as compounds or may be destroyed or decomposed.

The following minerals are eliminated in the bile after poisoning: antimony, arsenic, lead, manganese, mercury, phosphorus, silver, tin (Lussana), and zinc.

The following drugs are eliminated in the bile after an excess amount has been taken: atropine, bromide, cadmium (Marmé), caffeine (Strauch), curare (Lussana), essence of terebinthine (Cl. Bernard), iodine, iron chloride, menthol, phenol (Peiper), potassium bromide, potassium chloride (Isambert), potassium ferrocyanate (Bouley and Colin), potassium iodide (Cl. Bernard), potassium sulphocyanate (Peiper), quinine (Alberton), salicylic acid, sodium lactate, sodium salicylate, strychnine (Jacques), terpene, turpentine, and methenamine. Some drugs are eliminated in the bile after being taken in therapeutic doses. Thyroxin is eliminated in the bile after administration to rabbits, according to Elmer and Luczynski.

DYES

The following dyes are eliminated in the bile: acridine red, aniline blue, ammonium carminate, aniline red, Berlin blue, chlorophyll (Wertheimer), cochineal, Congo red (Lepehne), eosin, fuchsin (Husson), indigo carmine (Hatzieganu-Chrzon-szczewsky), methylene blue, neutral red, phenolphthalein, phenolsulphophthalein, phenoltetrachlorophthalein, rhubarb pigment (Heidenhain), sodium sulphindigo—if given intravenously (Diakonow), tetraiodophenolphthalein, and mercurochrome. Recently Matsuo has tested over three hundred dyes and has shown that the liver has a selective action for excreting some according to their structural formulas; the kidneys excrete others. Because the liver has this selective action on these dyes, some of them are used for liver-function tests.

BACTERIA AND TOXINS

Bacteria injected into the blood stream are frequently eliminated in the bile. *Bacillus prodigiosus* was found in the bile 1 hour following intravenous injection (Hess). *Bacillus tuberculosis* appeared in the bile of a guinea-pig 6 hours following intravenous injection. The bile constantly contained this bacteria 4 weeks after the injection of the pig (Perla). In rabbit's bile, tubercle bacilli were constantly present 3 days after intravenous injection (Calmette). It would seem that bile might be an excellent channel of exit from the blood stream for bacteria in various diseases. Some bacterial toxins are not acted upon in the liver but are excreted as such in the bile. Teisser found that diphtheria toxin was so excreted. Some toxins (tetanus) are neutralized by bile and then excreted, while in other instances the bile acts as a mediary in the production of antitoxins. Surely the presence of many live bacteria in the bile would alter the character of the bile in some way. A large variety of bacteria have been isolated from bile removed from the gallbladder at operation. The portal of entry, however, may be by way of the gallbladder wall or up the common duct. Further discussion appears later.

DECOMPOSITION

If bile constituents are decomposed, the following substances may be found in the bile: ammonia, cholic acid, *choloidique acide*, *dyslysine*, glycocoll, and taurin (Dastre). These substances are not normally found in bile.

Putrefaction causes marked changes in bile; and, on standing a sufficient time in nonsterile surroundings, the following substances, not present in normal bile, appear: acetic acid, ammonia, ammonium-magnesium-phosphate, ammonium sulphohydrate, calcium phosphate, hydrogen sulphide, sodium sulphate, valerianic acid, and volatile fatty acids (Dastre).

CHANGES IN BILE ON STANDING

Bile standing in an icebox for a considerable length of time becomes darker, and the nonfilterable portion settles to the bottom; the heavy sediment resembles powdered chalk, and the upper layer is more gelatinous. Injection of the filtrate disclosed a change in the toxicity value. When standing at room temperature, this same change takes place, but much more rapidly. In 48 hours the toxicity is doubled, and the color has changed to a darker brown. Ox bile permitted to stand at room temperature undergoes autolytic changes. There is a slight decrease in viscosity which is associated with an inconsiderable decrease in specific gravity. The pH changes rapidly, on standing, to a low H-ion concentration (Neilson).

Gallbladder bile can be kept for several days without any hydrolysis of the conjugated bile acids (Newman [1381]). The breaking-down of the conjugated bile acids normally in the human organism is unknown. Up to the present time, no such process has been demonstrated. Grossman claimed to have isolated a hydrolyzing enzyme from the kidney which can break down the conjugated bile acids to the simple bile acids. No proof has been offered that this ever occurs in either normal or pathologic conditions in the body; and it is possible that, when the unconjugated bile acids are excreted, the process is incomplete.

CHAPTER V

ORIGIN AND FATE OF BILE

IS BILE continuously formed throughout life? In obstructive jaundice what becomes of the bile? Does its accumulation in the body cause toxic symptoms? These questions involve the origin of bile, its usual course of distribution and activity, and its normal disposal. Consideration must be given to what happens when, in obstructive jaundice with the normal portal of exit blocked, there is a continued production of bile. The amount of bile normally secreted by man in 24 hours has been estimated as from 530 cc. (Wittich) to 940 cc. (Mayo-Robson). The estimate of 1,000–1,500 cc. per 24 hours is much too great (Lyon). If such a large amount of bile is continuously secreted, does it cause harm? The volume of secretion depends on many factors, such as diet and time of day, but not upon activity (1790) or blood pressure (Downs). There is a definite osmotic-pressure relation between the blood and bile. The blood, hepatic bile, pancreatic juice, and lymph, when measured by the Hill method, were found to be practically isotonic (Gilman and Cowgill). The injection of hypertonic salt solution intravenously causes a marked change in the blood, which is followed by parallel changes in the other body fluids, including bile. Water intake by mouth has little or no effect on bile secretion (Walzel and Weltmann).

The Golgi apparatus of the liver cell is concerned in the mechanism of secretion of bile. The bile constituents appear within the Golgi apparatus, which enlarges, fragments, and is discharged by way of the intercellular bile capillaries (Cramer and Ludford).

The complete failure to secrete bile has not been proved as compatible with life. Bile cannot be studied as a whole ex-

cept for volume and specific gravity. The great complexity of bile would involve almost endless work on the constituents. Bile is not only a secretion but also an excretion. Some work has been done with a few of the constituents: bile salts, bilirubin, and cholesterol. The bile-calcium relativity constant to 4 mg. per cent and potassium have no characteristic variations even with feeding (Leites and Koslowa).

ORIGIN OF BILE

Acholia has been referred to as the absence of bile. In complete obstruction of the common duct, bile fails to pass into the intestine. There is some evidence of even a complete failure of the liver to secrete bile in certain conditions, as in extensive chloroform poisoning with liver-parenchyma destruction or its later effects, shown by the failure of indigotate to stain the liver cells (Drury and Rous). Failure to obtain bile has been reported by Eppinger as being due to the blocking of the biliary capillaries by bile thrombi. This would still permit activity of the liver cells with removal of the products of liver secretion by the blood and lymph streams. There seems to be a real suppression of liver-cell secretory activity. This view has a large amount of evidence in its favor. Following the removal of an old obstruction to the common duct in man or dog, bile salts do not appear in the bile for approximately 8 days; bile pigments appear at once (Breusch and Johnston).

Whether or not the liver manufactures the constituents in the bile or merely excretes them is another question. That the selective removal of the bilirubin, bile salts, cholesterol, and other substances from the blood by the liver may be impaired or suppressed is very likely, as these substances have been repeatedly found in the blood stream in excess of those in the bile in the same person. It does not necessarily follow that they are reabsorbed after secretion by liver cells. The liver regulates the flow and concentration of bile. The effects of certain substances depend on whether they cause an increased outflow of already secreted bile or cause an actual

increased formation of bile constituents. Diminished secretion is caused by chloroform, ether, alcohol, veronal, atropine, pilocarpine, phlorizin, and quinine (Smyth and Whipple, Babbio and Zilocchi, Winogradow).

The work with various hormones is contradictory: Baltaceano, Vasiliu, and Paraschiv found that folliculin caused an increase in bile volume, bile salts, and cholesterol in female dogs; but Loeper, Lemaire, and Tauzin, using crystalline folliculin (made according to the Dosey method), intravenously caused a decreased bile flow in male dogs; corpus luteum extract (according to the Simonnet method) caused decreased intestinal activity and decreased bile flow; but when the two were injected together, there was intestinal paralysis and increased bile flow (?). Thyroid, splenic, mammary, orchic, ovarian, pancreatic, and thymic extracts are either inactive or very mild (Downs and Eddy, Tanaka).

Sterins, either rayed or unrayed, in the form of sistosterin, ergosterin, etc., have been reported as having various effects, which are not conclusive (Schönheimer, Higashi, Tanaka). Fever produced by the injection of termin or vaccine causes a diminished bile excretion, marked bilirubin concentration, and slight increase in total, residual, and amino nitrogen (Sugiu). Diathermy is a secondary cholaretic (Mitani) but has no effect on the diseased liver.

The parasympathetics in the rabbit are stimulated by pilocarpine, causing a decreased bile excretion, with increased total bilirubin excretion; the stimulation of the sympathetics by adrenalin causes no change; paralysis of the parasympathetics with atropine inhibits both the bile and bilirubin excretion (Saiki). Insulin and histamine cause increased bile secretion, while pituitrin and ergotamine have no effect (Leites and Isabolinskaja). But, according to Baltaceano, Vasiliu, and Paraschiv, the anterior pituitary body plays an important role in the secretion of bile. The quantity of bile is increased, and certain of the constituents are modified. Thyroid extract does not modify the bile excretion but

does cause an increased urinary nitrogen output (Smyth and Whipple).

BILE ACIDS

Bile acids normally are produced in man at the rate of 8–10 gm. in 24 hours (Stadelmann, Biedl and Krause, and Weintraud). There is normally a fairly constant endogenous production of bile salts (Whipple and Smith [2096]). They may be products of metabolism of the body or liver, modified and secreted, or just excreted by the liver. The taurin comes from the cystine of the food and body protein and appears in excess to combine with cholic acid. The precursor of cholic acid is unknown (Foster, Hooper, and Whipple). The site of origin of cholic acid, however, seems to be the liver, according to the work of Mann and McGath. Following extirpation of the liver, there is no detectable accumulation of bile acids in the blood.

A cholagogue is a substance that increases the volume flow of bile by causing contraction of the gallbladder muscles, resulting in expulsion of bile. Secretine, pilocarpine, histamine, acetylcholine and ergotamine are cholagogues (Brugsch and Horsters). Anticholagogues are substances which cause relaxation of the bile passages with decreased flow: hypophysin and atropine. A cholaretic is a substance that increases the quantity production of individual bile constituents: secretine and histamine (Brugsch and Horsters).

Bile acids are both cholagogues and cholaretics. The various bile acids have different quantitative and qualitative effects on the production of bile. Cholic acid is the active substance.

Bile-salt production can be increased in the dog with biliary fistula by feeding gelatin, tryptophan, and proline; either alone has no effect (Whipple and Smith). Tryptophan alone causes an increase in bile volume but no increase in bile-salt output. Tryptophan supplements gelatin and causes a marked output. Substances with similar structural formulas, such as indene, hydrindene, isatin, and indigo, do not have

a constant effect. Substances having a cholagogue action contain an indene, indol, or pyrrol ring. The feeding of taurin, cholesterol, erythrocytes, terpene hydrate, or camphor has no effect on bile-acid excretion (Foster). The feeding to dogs of glycoll and alanin causes an increased quantity as contrasted to quality excretion of bile, but lactic acid causes a decrease. The addition of bile acids causes a further increased excretion (Kawada). Liver, salmon-muscle, and beef-muscle feeding to dogs (Smyth and Whipple) causes a marked increase in output of the total bile acids: salmon causes 875 mg. increase; and meat, 1,470 mg. Proteose injection causes a decrease in the output, owing to liver parenchyma injury. Likewise an excessive application of Roentgen rays over the liver causes a diminution. Protein feeding in the form of meats causes an increase in bile-salt output in proportion to the amount fed. This output parallels the urine-nitrogen output, but the surplus of bile acids produced under normal conditions does not escape in the urine. The feeding of meat causes an increase in taurocholic acid output in the dog (Foster, Hooper, and Whipple). In a dog with Eck's fistula and a biliary fistula the bile-salt output is decreased, and the feeding of salmon now causes a greater decrease. Smith and Whipple conclude that the dog now is incapable of the production of the usual amount of bile salts and that there is a decreased cholagogue action.

The secretion of bile in rabbits is markedly decreased by feeding glucose, levulose, and honey. Large feedings almost cause acholia (Schwarz [1735]). In dogs with gallbladder fistula, glucose, peptone, and meat had no specific effect on the quantity of bile. Meat causes an increased concentration of bile, but glucose causes a decreased concentration (Leites and Jussin). There is rhythmical 24-hour variation of the glycogen content of the liver cells of the rabbit and functional output. The rhythmical formation of bile also occurs, which alternates with the assimilation of glycogen. The maximum

secretion for man and rabbit is during the day; the minimum, at night. Sleep causes a great reduction (Forsgren). There is twice as much bile formed in the daytime as at night (Waltzel and Weltmann). This periodicity has been observed in the human with gallbladder fistula with the minimum at 5:00-7:00 A.M. and the maximum at 11:00-1:00 P.M. (Josephson and Larson). This rhythmic functioning of the liver, alternating with bile secretion and glycogen production, does not parallel the blood-sugar curve or the urine-sugar curve and is not definitely related to food intake. Bile acids, given orally or subcutaneously, stimulate the deposition of liver glycogen in rabbits and dogs; bile acids act antagonistically to adenylypyrophosphate but similar to epinephrine. When cholic acid is used in large amounts, it has the reverse effect on liver glycogen. Sugar assimilation is aided by cholic acid in hyperglycemia with glycosuria, and even in pancreatic diabetes (Hasegawa, Kuramoto, Watanabe). Fasting causes a decreased output, but there is a minimum output even during long fasts, below which the bile-salt production does not go. Even a complete exclusion of bile ingestion does not markedly alter this bile-acid excretion. Whipple calls this the endogenous portion of bile-salt formation. Here probably catabolism of the body protein contributes to the bile-acid synthesis. *Bacillus coli* has no effect on the cycle of conjugated bile acids, according to Basu and Chakravarty. They used taurocholic acid. Although, when dehydrocholic acid was used in a nutrient solution with *B. coli communis* obtained from feces, Fukui was able to form 7-oxy-3,12-diketocholanic acid, when the culture was at 38° for 6 months. Licht used *B. coli*, proteus, typhoid, and pyocyaneus and found, after 14 days, no appreciable effect on bile acids in vitro. Streptococcus and staphylococcus have very little effect. Ultraviolet light has a marked effect on the sodium salts of bile acids and dilute bile from man, bear, and rabbit (Mikami).

Bile-salt feeding causes an increase in bile secretion and

bile-salt output. A dog with bile fistula was fed 21 gm. of bile salt, and the excess output was 13 gm. This quantitative output is not due to actual increased production but merely is absorption and re-excretion of the fed bile salt. Bile salt given by mouth or intravenously has the same effect on bile-salt output.

In obstructive jaundice the production of bile salts in the dog, based on calculations of the urinary sulphur from taurocholic acid, would indicate, with the onset of obstruction, the increased destruction of taurocholates. In a few days this destruction reaches a maximum, and then declines to the normal of that before ligation of the duct (Brakefield and Schmidt). If taurocholate is continually produced after ligation, as before, the sulphur output should continue high. But with the decline in sulphur to normal, either there is a failure to produce taurocholate quantitatively or other channels of disposal have become available.

A biliary fistula on each of 12 dogs was made by Cornejo-Saravia, and after 5-7 days a hepatectomy was performed. The bile acids were only slightly increased in the blood. Following the ordinary hepatectomy, the blood bile acids were markedly increased. He concluded that the bile acid increase found in the blood following simple hepatectomy was in the larger part derived from the intestine, owing to excretion prior to operation followed by absorption.

From experimental work with bile fistula dogs, Smyth and Whipple concluded that the liver produces bile salts. The dogs were given chloroform, which caused a reduction of bile-salt excretion to zero. (It is well known that chloroform destroys the liver parenchymal cells.) With repair of the liver damage the bile salt output returned to normal. This evidence does not seem conclusive, because the necrosed liver cells may fail to remove the bile salts from the blood rather than fail actually to produce them. Hepatotoxins, such as carbon tetrachloride, tetrachlorethylene, and phosphorus, cause a marked reduction in the production and concentration of

salts in the liver. That bile salts are formed in the liver parenchyma and not in the bile ducts was the conclusion reached by Whipple.

BILIRUBIN

The experimental works of Minkowski, Naunyn, Moleschott, Müller, and Stadelmann, employing various methods in determining the site of formation of bile pigments, led to the conclusion that bilirubin is formed exclusively by the liver. Virchow, in 1847, found bilirubin crystals in an echinococcus cyst and elsewhere. He questioned the site of formation of bile pigment. Many investigators have offered evidence to show that bilirubin is formed outside of, and without the aid of, the liver. The tests for bilirubin, however, were not sufficiently delicate to make very accurate determinations until after the quantitative diazo reaction was perfected.² According to van den Bergh, there are two types of bilirubin: the indirect, I, and direct, II. The indirect is formed in the blood stream (Aschoff) before reaching the liver. Crystals have been found in life in the vessels of the new-born, in brain plexes, and among the blood cells. The direct is an excretion form of the hepatic cells.

The literature up to 1928 on the formation of bilirubin was reviewed by Aschoff (81). A large amount of evidence has been accumulated to substantiate the belief that bile pigment is formed outside the liver, and further evidence shows that bile pigment is formed even with a complete abdominal evisceration of a dog (Mann); but no one has been able to prove definitely what portion of bilirubin is formed outside of the liver. It would appear that, wherever red blood cells are destroyed, hemoglobin may be changed over into bilirubin. Mann's experiments showed that a part of the bilirubin in the bile is of extrahepatic origin: from muscle pigment, blood pigment, and absorbed animal and plant pigments. Within 6 hours following hepatectomy the plasma became yellow, and continued to increase in color until death. Icteric

² The van den Bergh test is not absolutely specific for bilirubin.

coloring of the sclera and mucous membrane appeared in about 16 hours. At autopsy even the body fat gave a positive test for bilirubin.

Bile pigments originate from hemins, according to Lemberg. The hemins are changed to green hemins, then to biliverdins, then to dehydrobilirubin and reduced to bilirubin. The reduction from biliverdin to bilirubin takes place in the tissues. Under anaerobic condition biliverdin is changed to bilirubin by all the tissues of the guinea-pig except by skin—the best by liver. The liver enzymes of all liners investigated were active, including the frog's. Lemberg concluded that biliverdin is a primary bile pigment and that bilirubin is a reduction product. This bilirubin always gave a direct reaction. Two grams of hemoglobin were prepared from erythrocytes by Sribhishaj, Hawkins, and Whipple and were injected intravenously into dogs with renal gallbladder fistula; 90 per cent of the calculated increased bilirubin was eliminated. Theoretically, 1 gm. of hemoglobin makes 40 mg. of bilirubin. The amount of hemoglobin injected was below the renal threshold for hemoglobin. Hemolyzed blood in defibrinated blood was passed through an isolated spleen of a dog by a perfusion apparatus for 4–5 hours, by Ernst and Szappanyos. Bilirubin in the blood was increased, and they concluded that bilirubin can be formed outside the liver. Negative results were obtained when the kidney and lungs were perfused. Bilirubin is also formed by the action of splenic extract on a hemorrhagic exudate. Several kinds of bacteria have no effect on the formation of bilirubin from hemoglobin. They believed that bilirubin is formed by ferments in the reticulo-endothelial cells and that the bilirubin of the hematoma is not of extracellular origin.

Large amounts of bile were fed to animals by Hooper and Whipple (837) without effect on the bilirubin content of the fistula bile. They concluded that there is no absorption of bilirubin from the intestinal tract. On the other hand, Royer found that, when he fed bilirubin to dogs, there was an in-

crease of bilirubin and urobilin in the blood and bile. There was more bilirubin in the mesenteric vein than in the aorta. The intravenous injection of urobilin caused an increased urobilinocholia. He concluded that there is a reciprocal effect of bilirubin and urobilin in the blood and their elimination in bile.

Sheep's bile was fed to bile fistula dogs by Broun, McMaster, and Rous (269). This bile contained cholohe-matin, a substance which has a characteristic spectrum and is therefore easily identified in the bile. Cholohe-matin was excreted in the bile in varying amounts. This variation was due to the gastrointestinal disturbances caused by an excess of bile interfering with absorption. By deduction they concluded that bilirubin, a similar pigment, is absorbed from the intestinal tract.

No difference was found by Bollman, Sheard, and Mann in dogs in the bilirubin content of the blood in the mesenteric veins and arteries following intestinal administration of 100-200 cc. of fresh gallbladder bile. Rose bengal, mixed with bile and put into the intestine, appeared in greater concentration in the blood of the mesenteric vein than in the arterial blood. One to 2 cc. of bile given intravenously caused a definite increase in the bilirubin content of the blood. Therefore they concluded that bilirubin is not absorbed from the intestine. They used the spectrophotometric method.

Bile-pigment output decreases in secondary anemia in dogs with renal-bile fistula. This decrease is parallel with the anemia, according to Hawkins and his associates. When hemoglobin is injected, there is a quantitative increase of hemoglobin and also, strangely, a quantitative return of bile pigment. They concluded that the body can synthesize the pyrrhol nucleus in an emergency such as anemia. In a study of 78 cases of pernicious anemia by duodenal drainage, Schneider found the bilirubin and urobilin increased but the urobilinogen unaffected. Royer and Speroni injected intravenously 2 mg. of urobilin per each 5 kg. of body weight in

three humans who had been cholecystectomized, and found in the duodenal drainage an increase of bilirubin of five times the normal and urobilin from thirty-two to forty-eight times.

CHOLESTEROL

Cholesterol is excreted in the bile of man at a fairly constant rate of 6-7 gm. in 24 hours (Roger), in dogs 0.5-1.0 mg. per kilogram in 24 hours. Cholesterol in part comes from the epithelium of the bile passages, but a larger part is excreted by the liver. It is generally considered an end-product of metabolism. It is closely allied to cholic acid chemically and originates from cholestane, an isomer of pseudocholestane, from which latter the bile acids are derived (Windaus, Wieland). That the liver actually secretes cholesterol is shown by comparing the blood value, which is 0.44-0.75 parts per 1,000 and the bile value 1.6 parts per 1,000. Much evidence has been offered to show that cholesterol is absorbed from the intestine, but at the present time this evidence is not entirely conclusive. There is some basis for the idea that the amount of cholesterol in the blood parallels the amount excreted in hepatic bile. Cholesterol output is increased when a dog or rabbit is given a diet rich in cholesterol; fasting causes a decrease in bile cholesterol (McMaster, Kusaka). Rabbits fed fat-soluble vitamin cod-liver oil and biosterin produce an increase of cholesterol in the blood and bile, as calculated by the Bloor method. The liver keeps the blood cholesterol constant by excreting the excess from the blood stream into the bile (Kusaka). The increase in bile cholesterol has no relation to bile quantity (McMaster). Bile salts given by mouth cause an increased output; isatin and decholin have no effect; while liver destruction by chloroform causes a greatly decreased output. Cholesterol and bile salts run a close parallel, and there is a question of their physical relationship (Wright and Whipple). Others do not think there is any parallelism of cholesterol, bile salts, and

bilirubin. Determination of the origin, fate, and function must await further developments in chemistry.

LECITHIN

In pernicious anemia there is an increase of lecithin to 165 mg. and a decrease in pregnancy (Barat). Given subcutaneously and intravenously to rabbits, it causes an increased output in the bile. When given intravenously, the output is much greater than when given subcutaneously. Oral administration of bile acids causes the blood lecithin to decrease and the bile lecithin to increase in amount and concentration. Therefore the liver regulates the amount of lipoids in the blood by excreting them in the bile (Asoda).

FATE OF BILE

BILE ACIDS

The amount of bile acids manufactured in the human body has not yet been definitely determined. The quantity (8-10 gm.) excreted in fistula bile in man and dog has been observed repeatedly. If bile salts were continuously produced at the normal rate, there would soon be an enormous excess in the body, following complete obstruction of the common bile duct.

In obstructive jaundice the urine contains a small amount of bile salts, as shown by the Pettenkofer test; but certainly 8-10 gm. is never excreted in this manner. The test reveals a small amount, and frequently it is entirely negative. Since such a small amount is actually excreted in the urine, some workers have concluded that the bile acids are broken down in the blood stream and other tissues, and then excreted as other substances. There is no adequate experimental work to support these ideas. Recently Chabrol determined the fate of cholic acid injected into the blood stream of the dog at the rate of 0.06 gm. per hour per kilogram of weight. A total of 6.10 gm. was given; 5.41 gm. was eliminated in the bile, 0.261 gm.

in the urine, and the rest was fixed by the tissues, within $\frac{1}{2}$ hour following the intravenous injection.

The influence of the liver on the destruction of bile salts was shown by Bollman and Mann with the (1) ligation of the common duct, (2) extirpation of the gallbladder, and (3) removal of the liver of the dog. With (1) and (2) a very small amount of bile salts was excreted in the urine the first day; 500 mg. daily were excreted the second day and thereafter. After feeding 1-2 gm. daily, there was no increase in the urine; but following intravenous injection of the same amounts, 50 per cent was recovered in the urine. They concluded that the body can destroy fixed amounts of bile salts. When the liver was removed (3), the bile salts excreted in the urine were not in large enough quantity to be shown by the Gregory method. Intravenous injection of bile salts was followed by almost complete recovery of them in the urine. Bollman and Mann further concluded that the destruction of bile salts does not occur in the absence of the liver.

A negative Pettenkofer test and normal values for the sulphur and nitrogen in the urine following the feeding of taurocholic acid indicate that the urine is not the normal channel for the elimination of bile acids (Schmidt and Clark). Schmidt and Merrill examined the urine in jaundice and found that only a few hundred milligrams were eliminated in 24 hours. But in contrast to this was the finding of taurin unchanged in the urine.

Using dogs with complete bile fistula, Stadelmann gave to them, by mouth, 2 gm. of bile salts dissolved in 100 cc. of water. One hundred and thirty cubic centimeters of bile were secreted with 4.11 gm. of bile salts. The urine gave a Pettenkofer reaction after 12 hours. Ox gall and sodium glycocholate (Merck²) were fed with the same results. Stadelmann concluded that bile acids given by mouth are excreted in large measure by the liver. Ox gallbladder bile and dog bile

² Manufacturer.

caused an increased output. The glychocholic acid fed was excreted in part as such in dog bile.

The fate of bile acids has been carefully studied by Brakefield and Schmidt by ligating the common duct in dogs and examining the urine for bile acids and bile pigment. The quantity of bile acids excreted in the urine decreased with time and finally became very small. Then the feeding of taurocholic acid caused an increase in the excretion of taurocholic acid, but the bile pigment held a constant low level. The feeding of a small amount of taurocholic acid to dogs caused an increased excretion in the biliary-fistula bile of taurocholic acid (calculated by the NH_3 method), representing about 90 per cent of the intake in the first 4 hours. When this was repeated on succeeding days, there was an increased secretion of bile in proportion to the taurocholic-acid intake. The same was true with sodium taurocholate. If, however, cholic acid were fed, there would be a gradual decrease in the taurocholic-acid output, presumably in direct proportion to the supply of taurin available, for when taurin was supplied in the food the excretion was increased and maintained. What happens to the cholic acid when there is no output is still undetermined, but from other work it is known that toxic symptoms rapidly develop and eventually result in death.

It would appear from the experimental work with the fistula dogs of Foster that bile acids are absorbed rapidly when fed and likewise are rapidly excreted in the bile, and that the amount of bile acids excreted are dependent on the cholic acid available, and in the dog also on the supply of taurin. The process of absorption and elimination was usually continued less than 6 hours. Any toxic process set up in the organism should be well limited to that period.

Bile acids diffuse from, or are absorbed from, the intestine via the portal blood and then pass to the liver, according to Josephson and Rydin in experiments on the horse, rabbit, and cat. Choleic acid is decomposed into fatty acids and bile acids immediately after passing the epithelial layer of the

mucosa, then the two substances take different routes—the bile acids the portal, and the fatty acids the lymph, channels. When sodium cholate and sodium glycocholate were given by mouth, the bile acids in the portal blood were tripled and the heart blood showed only a trace. Josephson and Rydin think that bile given orally will probably never appear in the peripheral blood if the liver is undamaged.

In obstructive jaundice, if synthesis of bile acids takes place normally, then the possible fate is: (*a*) absorbed into blood stream and excreted quantitatively in urine; (*b*) absorbed into the blood stream and then one part broken down and another part excreted in the urine; (*c*) absorbed into the blood stream and broken down completely in the blood and tissues; (*d*) wholly or partially stored in tissues. If a large part of the taurocholic acid is broken down, there should be a large increase in urine sulphur. This has not been proved.

In jaundice there is a decreased ability to conjugate benzoic acid, and the liver undergoes pathologic changes in obstruction of the common duct. If it is assumed that taurocholic acid is synthesized by the liver, the decreased output of this acid sometime after the onset of jaundice may be attributed to its decreased synthesis rather than to its breaking-down.

BILE PIGMENTS

The bile pigments are normally excreted into the intestine (McMaster and Rous, McMaster and Elman). Part of the pigment is changed to urobilin and urobilinogen, reabsorbed, and then excreted in the urine; a second part is changed to stercobilin and passes out with the feces; a third part is probably absorbed again as bilirubin and biliverdin to be used in the formation of hemoglobin. Details of this work are given elsewhere.

In pathologic conditions, such as obstruction of the common duct, the production of bilirubin continues, as is evident by the increasing accumulation of it in the body tissues.

Pigment has been found in the urine, sweat, tears, saliva,

and in the tissues as bilirubin or biliverdin; also in pathologic fluids as pericardiac, ascitic, and joint fluids.

The affinity of bilirubin for the erythrocytes has been shown by Saeki and Maeda. The speed of adsorption is increased with fever. The mechanism is in part a chemical combination, and the red cells increase in volume on taking up the bilirubin. The red cells of different animals differ in their capacities for taking up bilirubin.

Bilirubin was given intravenously by Saiki (1669) to rabbits and dogs. When the reticulo-endothelial cells were blocked with colloidal solution of silver and India ink, the excretion of the bilirubin in the bile was not interfered with. But when the parenchymal liver cells had been disturbed by hepatotoxin, there was a delay in the disappearance of the bilirubin from the blood stream and also a diminution in the output of bilirubin in the bile in proportion to the amount of parenchymal liver damage (Tada). Bilirubin is excreted by the epithelial cells of the urinary canals of the kidneys. The liver and kidney act under stress reciprocally (Saiki). Bilirubin was given intravenously to rabbits and dogs by Saiki; much was excreted in the bile, less in the urine, and very little was found in the spinal fluid. The bilirubin excretion by dogs' kidneys was much greater than by rabbits' kidneys.

In obstructive jaundice, the formation of bilirubin is normal; but as it cannot be excreted in the bile, it therefore accumulates (Aschoff). The fate of bilirubin in the intestine has not been definitely determined. Sackey, Johnston, and Ravdin found no loss by absorption in the jejunal loop of dogs and no loss by conversion to urobilin by the juices from the entire small intestine. The disappearance of the pigment remains to be answered. Watson fed 10 mg. of crystalline bilirubin to two persons with complete obstruction of the common duct by neoplasms. Absorption from the intestine was undetected, and the urobilinogen was not accounted for in the feces and urine; but there was obtained from the stools stercobilin crystals which were not present before. Scholder-

er found that 10 per cent of the injected quantity of 1-2 mg. pure bilirubin (Schuchardt³) was absorbed in 1-2 hours from the isolated intestine of the rat. The absorption rate was increased by bile acids.

The evidence that bile salts have an enterohepatic circulation (Schiff) seems satisfactory; but the cycle of bilirubin (1241), cholesterol, and vitamins (1170) needs further confirmation. At the present time there is no general agreement as to which substances in bile are purely waste products and which are conserved.

CHANGES OF BILE IN THE GALLBLADDER

The concentration of the different constituents in the gallbladder are much different from fistula or hepatic bile. The gallbladder absorption produces a solution four to ten times more concentrated. The absorbed material is chiefly water and inorganic constituents (Ivy). The bilirubin is concentrated even to 44.8 times, and the bile acids 3.7 times; a part of the bile acids is absorbed (Rosenthal). The bile ducts do not concentrate more than two to three times, and the inflamed gallbladder does not concentrate the bile at all (Ivy).

Recent experimental work on the gallbladder of a cat, done by Winkenwerder, showed that the epithelium of the entire extrahepatic system, with the exception of the small ducts, is permeable to crystalloids, potassium ferrocyanide, and ferric ammonium citrate. The blood vascular system is the resorptive pathway for the crystalloids after having passed through the epithelial cells. The lymphatic system is not the medium of transportation for these crystalloids. With the excretion of their mucin, the epithelial cells of the gallbladder undergo structural changes and become more permeable to Prussian blue. The gallbladder does not absorb lecithin and cholesterol but does readily absorb sodium and chloride; other substances are absorbed in different degrees.

In some diseases of the gallbladder some constituents, such

³ Manufacturer.

as bilirubin and bile acids, are absorbed more rapidly, even causing jaundice (Blond, Colp, Riegel). With the selective absorption, infection, and changed pH and osmotic status, scarcely soluble substances, such as cholesterol, protein, bilirubin, albumin, and phosphates, may be precipitated (Lichtwitz, Rosenow, Patey). A change in the reaction between calcium and phosphorus and bicarbonate may cause their precipitation (Lichtwitz). Sodium chloride and bicarbonate are readily absorbed (Ravdin). There is no evidence that calcium is secreted by the normal gallbladder wall; but it may be if the wall is damaged, as shown by the deposits in the wall (Johnston). The concentration of bilirubin in human gallbladders obtained at necropsy and surgical drainage was from 3.5 to 1,786 mg. per 100 cc. (Elton). In a damaged gallbladder Riegel, Ravdin, and Johnston found the bile salts absorbed, a decrease in the concentration of the solution, and the cholesterol content mixture increased. In thyrotoxicosis the cholesterol in the gallbladder and liver bile is increased and the bile acids are decreased; in hypothyroidism the reverse is found (Gobler). Cholesterol, put into the dog's gallbladder by way of a catheter in the cystic duct, is absorbed by the gallbladder mucosa (Rousselot and Bauman). Human gallstones, 77 per cent cholesterin, were put into a dog's gallbladder; in from 6 months to 1 year all fragments were dissolved. In dogs with cholecystitis the stones were still present (Harley and Barrett in 1903). This work was repeated by Saiki, who found the stones dissolved in 186 days when the dogs were on a complete ration; but when deprived of vitamin D, the stones were enlarged.

Pregnancy and puerperium exert an unfavorable influence on bile secretion. The ovary, present or absent, has no influence on bile secretion (Tominaga). The effect of the diseased ovary has not been determined. Thirty-four specimens of gallbladder bile were examined in pregnancy at term by Riegel, Ravdin, Morrison, and Potter. The cholesterol concentrations were from 130 to 1,000 mg. per 100 cc.; all

but three concentrations were above 200, and eighteen were above 300. The bile salt was decreased in every instance. The highest, 4,690 mg. per 100 cc., was about one-half that found in normal gallbladders. The chloride, calcium and phosphorus were within normal limits. Potter did not find such wide variations in his 390 cases where bile was removed at Caesarean section, although the cholesterol values were high and the bile salt low. Bacteria were present in several cases.

CHAPTER VI

TOXICITY OF BILE ACIDS

BILE ACIDS AND THEIR SALTS

THE principal bile acids in the bile of man are glycocholic acid and taurocholic acid. They occur in the form of sodium salts. Other bile acids have been demonstrated, but their quantity is unimportant in comparison with these two. There is approximately three times as much sodium glycocholate as sodium taurocholate in human gallbladder bile (Trifanowsky) and fistula bile (Yeo and Herroun). The total amount of bile salts secreted in man in 24 hours is 11 gm., according to Voigt, and 10 gm., according to Stadelmann; in dogs, 4 gm. (Bidder and Schmidt). Bile salts are found in the normal human blood, according to the modified Pettenkofer test, from 2.6 to 6 mg. in terms of glycocholic acid to each 100 cc. of blood (Rowntree). This latter value has been seriously questioned because the Pettenkofer test is not specific for bile acids. There has been considerable discussion as to the exact nature of the bile acids in the blood stream, but in these experiments it is assumed that the bile acids in the blood stream are in the form of free conjugated bile salts.¹

The total quantity of bile secreted in 24 hours is between 500 and 1,000 cc. (Hammarsten).

Complete acholia is unknown in human pathology. Hypocholia is found in some disturbances of the liver. Polycholia appears to occur in both man and experimental animals. The liver is normally able to secrete bile of different salt concentrations, as shown by preceding experiments; but in fistula bile in dogs the usual range of variation in the concentration

¹ The terms *bile acids* and *bile salts* have been used interchangeably by almost all investigators. Bile acids are usually insoluble in injection menstruum; so they are injected as the sodium salts of the respective bile acids.

of bile salts is very slight. Clinical observations show that the liver does actually secrete a "white bile" which is of hepatic origin.

It is rather difficult to compare the toxicity of the various bile acids. Many of them have been prepared in extremely pure form, but taurocholic acid² has not. Some bile acids have been purified in minute quantities but are not available for experimental purposes in sufficient quantities. Some of the divers conclusions drawn by various investigators may be explained by the fact that they worked with impure product.

For almost a hundred years a controversy has raged as to which substance in bile causes the toxic symptoms. In 1840 the toxicity was attributed by some investigators not to bile itself but to "impurities" in bile, which caused capillary thrombi. Bouisson, as previously stated, made parallel experiments, using filtered and unfiltered bile. He reported that filtered bile was nontoxic. Then the whole question as to toxicity was in doubt when Henle, in 1847, wrote his *Pathology*. In 1848 Strecker discovered the bile acids, and immediately investigators attributed all the toxicity to them. Frerichs, De Bruin, Bouchard, Lugli, Plaesterer, Bowler, King and Stewart, Prévost and Binet attributed the greater toxicity to bilirubin; but practically all of these men worked with impure

² Taurocholic acid was received from a number of chemical houses and laboratories in the United States and Europe, commercial products varying in degree of purity from 40 to 85 per cent. The purest product was certainly very much less than absolute purity. The products received varied from deep orange-yellow to yellow in color. The powder did not flow freely in the bottle and either was or became a hard, gummy mass. Microscopic examination did not show typical crystals. One extremely pure product was seen in the laboratory of physiological chemistry of the University of Chicago, which, according to the formula, contained the exact amount of sulphur. This preparation was almost pure white with but a faint yellow appearance. The quantity was not sufficient for experimental purposes. Numerous attempts were made to bring the commercial products to the same degree of purity but were always accompanied by failure. The writer, therefore, assumes that all these experiments referring to taurocholic acid were made with crude products and are not entirely reliable.

Recently, 1937, at Columbia University, Cortese and Bashour claim to have synthesized taurocholic acid from triformylcholic acid and taurin. If this synthetic form is pure, identical with the natural form, and more staple, which they claim, it may be the means of clearing up some of the confusion concerning taurocholic acid.

chemicals or drew their conclusions from indirect work, as from filtered bile. The discussion of bilirubin is given in a separate section.

Greater toxicity was assigned to the bile salts by Röhrig, Feltz and Ritter, Legg, Rywosch, Greene, Aldrich and Rown-tree, Eilbott, Quincke, Stadelmann, Emerson, von Dusch, Bickel, Still, and Horrall. From the evidence we conclude that bilirubin is nontoxic and that the bile acids are toxic. The toxicity of bile varies almost directly with its salt content and specific gravity, as evidenced by the fact that gallbladder

| | Minimum Fatal | Lethal Dose |
|----------------------------|------------------|-------------|
| Sodium dehydrocholate..... | 1.00 | 1.10 |
| Sodium taurocholate..... | 0.10 | 0.11 |
| Sodium glycocholate..... | 0.08 | 0.09 |
| Sodium apocholate..... | 0.07 | 0.09 |
| Sodium cholate..... | 0.05 | 0.05 |
| Sodium desoxycholate..... | 0.01 | 0.015 |

bile has a greater toxicity than hepatic-duct bile or fistula bile (Colasanti, Lugli).

Sodium taurocholate was considered by Stadelmann (1826)³ to be ten times more toxic than sodium glycocholate. Red blood cells were destroyed by a solution 1:600 of the former, while 1:50 of the latter gave a comparative result. Feltz and Ritter (566) used the same method and concluded that sodium taurocholate is more toxic than sodium glycocholate. Gillert tested the relative toxicity by intravenous injections in rabbits and found sodium taurocholate to be one-eighth more toxic than sodium glycocholate. The fatal dose of bile salts in rabbits, in terms of grams per kilogram of body weight, is shown in the table above.

No difference in the toxicity of the two main salts was found by Meltzer and Salant in their experiments with frogs. Emerson obtained commercial products of sodium glyco-

³ P. 56: "Taurocholsaure hat eine grossere toxische wirkung als Glycocholsaure."

cholate and sodium taurocholate, recrystallizing them three times, forming fine white powders with a melting-point of 150° C. for sodium glycocholate and 95° C. for sodium taurocholate. These bile salts were dissolved in distilled water, making 3 per cent solutions, which were injected into the femoral veins of dogs. The injections were continued at a uniform rate of speed until the lethal dose had been given. Blood pressure and respiration tracings were taken. He found that the average lethal dose for 10 dogs each was as follows:

| | |
|--|-------------------|
| Sodium glycocholate..... | 8.5 cc. per pound |
| Sodium taurocholate..... | 10.1 |
| Ox gallbladder bile (diluted with equal amount of normal salt)..... | 6.8 |
| Ox gallbladder bile (with pigment removed) | 7.3 |

Emerson is almost alone in the belief that sodium glycocholate is more poisonous than sodium taurocholate.

The action and toxicity of sodium glycocholate and sodium taurocholate have been studied extensively by Rywosch. He found that sodium taurocholate inhibits coagulation of the blood more readily than sodium glycocholate and acts more energetically⁴ on excised muscle of both warm- and cold-blooded animals. His findings on the relative toxicity of the two salts showed the fatal dose for frogs to be: sodium glycocholate, 100 mg.; sodium taurocholate, 60–70 mg. The lethal doses for frogs of 40–50 gm. weight, by subcutaneous injections of various salts, are:

| | |
|--------------------------|----------|
| Sodium chenocholate..... | 0.05 gm. |
| Sodium taurocholate..... | .06 |
| Sodium cholate..... | .08 |
| Sodium choloidinate..... | .07 |
| Sodium hyocholate..... | .10 |
| Sodium glycocholate..... | 0.10 |

⁴ Rywosch (1658): "Energetically is a literal translation of 'Energischer' which really means stimulates first then causes necrosis of the muscle tissue. When a one-half per cent solution of bile salts is placed on a muscle at first there is strong convulsion, then a shrinking of the muscle and transformation. Under the microscope its cross striations are lost and it is entirely coagulated. If examined just before the striations have disappeared they appear in uneven waves or in staircase formation."

The toxicity, determined by the concentration necessary for complete solution of cattle erythrocytes, by Rywosch, is:

| | |
|--------------------------|-------|
| Sodium chenocholate..... | 1:700 |
| Sodium taurocholate..... | 1:600 |
| Sodium choloidinate..... | 1:500 |
| Sodium cholate..... | 1:200 |
| Sodium hyocholate..... | 1:200 |
| Sodium glycocholate..... | 1:50 |

From intravenous injections in the dog, intraperitoneal in the rat, and intralymphatic in the frog, Still (1841) rated choleic acid most toxic, desoxycholic acid second, glycocholic acid next, and cholic acid least toxic. Cholic acid is very poisonous, and hyocholic and choloidinic acid less poisonous, for the protoplasm of both plant and animal (Macht, Grollman, and Hyndman). Von Dusch found that sodium cholate dissolves red blood cells as rapidly as sodium glycocholate. He assigned the toxicity to the cholate portion of sodium glycocholate and sodium taurocholate. Bouchard and Tapret, and De Bruin (233), measuring the toxicity by intravenous injection in rabbits, reported that sodium cholate 0.54 gm. per kilogram of body weight is sufficient to kill, and that sodium cholate 0.45 gm., sodium taurocholate 0.46 gm., and bilirubin 0.05 gm. per kilogram of body weight are fatal.

Comparative tests on excised frog's heart were made by Wieland (2110), who found the relative toxicity for molecular solution:

| | |
|------------------------|--------|
| Cholic acid..... | 1:800 |
| Desoxycholic acid..... | 1:6400 |

Subcutaneous injections of 10 per cent water solution showed desoxycholic acid eight to nine times more toxic than cholic. Wieland standardized the hemolytic power of two bile acids for cattle red blood cells, observing complete solution:

| | |
|------------------------|----------------|
| Oleic acid*..... | 1 |
| Desoxycholic acid..... | 1/25 as toxic |
| Cholic acid..... | 1/250 as toxic |

**Oleinsäure* means oleic acid. Wieland (2110, p. 91): "Oleinsäure ist für gewaschene rote Blutkörperchen etwa 25 mal so giftig wie Desoxycholsäure und 250 mal so giftig wie Cholsäure."

The lethal dose for guinea-pig by subcutaneous injection, according to Neubauer (1367), is:

| | |
|----------------------------|-----------------|
| Sodium dehydrocholate..... | 4.4 gm. per kg. |
| Sodium cholate..... | 0.5 |
| Sodium desoxycholate..... | 0.5 |

Intravenous: sodium dehydrocholate:

| | |
|--------------|--------------------------|
| For dog..... | 3.6 gm.; no toxic effect |
| For man..... | 3.0 gm.; no toxic effect |

For hemolysis of erythrocytes in salt solution:

| | |
|----------------------------|---------------|
| Sodium dehydrocholate..... | 0.63 per cent |
| Sodium desoxycholate..... | 0.04 |

He concluded that in the blood stream the protective action of serum is so high that the hemolytic point would never be reached in jaundice.

Working with the sartorius muscle of male frogs, Tsuruta (1950) found that the minimum toxic concentration of bile acids necessary to produce tetanus is:

| | |
|--------------------------------------|------------------------|
| Cholic acid (as sodium cholate)..... | 0.18 per cent solution |
| Sodium desoxycholate..... | 0.04 |

The amount of antagonist necessary to prevent tetanus varies with the kind of bile salt. Cholic acid requires an equal weight of phospholipid, and desoxycholic acid nine times as much as its own weight.

The relative toxicity of bile salts, according to their hemolytic action on red blood cells of cow, was determined by Bayer (130). The concentration necessary to cause complete hemolysis is:

| | |
|------------------------|--------|
| Cholic acid..... | 1:200 |
| Desoxycholic acid..... | 1:1930 |

Shoda found complete hemolysis caused by:

| | |
|-----------------------------|--------|
| Desoxycholic acid..... | 1:2560 |
| Gallodesoxycholic acid..... | 1:2560 |
| Hyodesoxycholic acid..... | 1:1280 |

Okamura (1407) found toad bile acid the most hemolytic of all bile acids for rabbits' erythrocytes:

Bufodesoxycholic acid..... 1:3200

Kaziro and Tsuji:

| Kind of Acid | Kind of Erythrocytes | Proportion |
|------------------------|----------------------|------------|
| Desoxycholic..... | Human | 1:3000 |
| Apocholeic..... | Human | 1:1500 |
| Cholic..... | Human | 1:750 |
| Desoxycholic..... | Goat | 1:2560 |
| Chenodesoxycholic..... | Goat | 1:2560 |
| Hyodesoxycholic..... | Goat | 1:1280 |
| Ursodesoxycholic..... | Goat | 1:320 |
| Bufodesoxycholic..... | Rabbit | 1:3200 |

Hemolysis varies with the pH and with the concentration of the lysin. If the bile solution is more acid than pH 6.0, there is increased hemolysis; likewise a higher concentration of alkalis will accelerate the systems (Gordon).

Andrews and Aronsohn determined the effect of bile salts on the gallbladder when introduced by way of a catheter. The salts are arranged in order of effect:

Desoxycholic acid.....Very severe effect
 Apocholeic acid.....Severe effect
 Cholic acid.....Less severe effect
 Dog bile.....Less effect
 Hydrolyzed bile salts.....Some effect
 Commercial bile salts.....Little effect
 Glycocholic acid.....Slight effect
 Dehydrocholic acid.....No effect

The effect of changing a bile acid to a dehydro-form is illustrated by apocholeic and dehydroapocholeic acids. The surface tension of the sodium salts are:

| Percentage | Apocholeic Acid | Dehydro-apocholeic Acid |
|------------|-----------------|-------------------------|
| 1..... | 691 | 697 |
| 0.25..... | 708 | 800 |
| 0.10..... | 737 | 862 |

Apocholeic acid is more hemolytic than its dehydro-form; it is about twice as toxic for rats when given subcutaneously. The choleric action, however, is in the reverse order: most active, dehydroapocholic acid; next, dehydrocholic acid; and least, apocholic acid (Adlersberg and Lustig).

Choleic acid enteroliths have been reported in seven cases, according to Hellström. Chemical analysis has shown they are made up of a free biliary acid, choleic acid. Hellström said that they were formed in the intestine. The toxicity of choleic acid in these cases was undoubtedly modified in some other manner.

A large variety of other bile acids occurs in small amounts in man and other animals, some of which are modified forms of commonly known bile acids. For example, anthrodesoxycholic acid and chenodesoxycholic acid are found in man; gallodesoxycholic acid is found in the hen and goose; lithocholic acid in the ox; and phocataurocholic acid in the walrus. Their toxicity is unknown.

Von Dusch, Röhrig, and Leyden each concluded that the activity of the bile salts is not entirely due to the cholic-acid part of the molecule. It is increased by the conjugation. Each found that sodium taurocholate is four times more toxic than sodium cholate, and sodium glycocholate four times less toxic than sodium cholate. Therefore, there is some influence due to the combination of taurin or glycoll with cholic acid; otherwise, all three would have the same toxicity. Rywosch found that this combining process modifies the action but not entirely either quantitatively or qualitatively. Gallbladder bile and bile obtained by duodenal tube from man is lethal for rabbits in quantities of 0.4 cc. per kilogram of body weight. The same bile, when aged, is much less toxic than the recently drawn bile (Antitch).

Bile acids greatly accelerate the action of the pancreatic juice on esters. The hydrolysis rate is increased many times by the addition of bile to the pancreatic juice, since bile and pancreatic juice together are much more toxic than either

by itself. No theory of this interaction has been advanced to explain the actual mechanism satisfactorily.

No change in toxicity of sodium taurocholate is found when the pH is kept within the limits of 5.8 and 7.4. The minimal mortal dose was determined for rabbits administered by intrapleural route and intravenously (Schiaparelli).

Human serum diminishes the toxicity of bile salts. Injected intraperitoneally, it requires double the amount of sodium taurocholate when used with serum than when used with salt solution, to kill white mice. Hemolysis is produced by 0.625 per cent bile salt in sodium chloride but requires 2.5 per cent when used with human serum (Williams).

The toxic action of bile salts seems to be very highly specific in that the degree of action varies considerably with the different forms of bile acids. Some bile acids, such as desoxycholic, in very small amounts, will cause gastric ulcer, while other bile acids are more prone to cause hemolysis. The inhibiting substances for these different actions is also very highly specific, as the delay of blood coagulation caused by bile salts can be checked by glucose, but the inhibition of the hemolytic action of bile is best prevented by sucrose. The lipides antagonize bile salts in ulcer formation and also inhibit the hemolytic action of the bile salts in gastric-ulcer formation (Tsuruta, Bayer). Nothing is known of the mechanism of these actions.

The action of bile salts on egg albumin and collodion ultrafilters is such as to decrease the permeability. Sodium taurocholate and sodium glycocholate, 1/1,000 solution, have the same action (Nattan-Larrier).

Bile salts act as toxic substances by inhibiting the oxygen consumption of the tissues (Strain and Marsch) and by inhibiting autolytic protein metabolism (Karasawa). On the other hand, nuclein-splitting in extract of bull testicle is increased by the addition of cholic acid (Tanaka). The respiration of rat tissue is prevented by sodium cholate, sodium glycocholate, and sodium taurocholate, in decreasing order

of toxicity (Terao). The critical inhibitory concentration of the bile salts for the consumption of oxygen by various tissues is as follows, according to Strain: sodium cholate and sodium desoxycholate, 1 mM for spleen, liver, and kidney; sodium glycocholate, 2 mM for spleen, 4 mM for liver, and 5 mM for kidney; and for sodium taurocholate, 4 mM for spleen, 8 mM for liver, and 10 mM for kidney. Using the respiration of cells as a measure of toxicity, the conjugated bile acids are less toxic than the unconjugated (Strain and Marsch).

TAURIN

Taurin is an important amino acid which combines with cholic acid, forming taurocholic acid. It may be found free in the bile (von Gorup-Besanez), blood, or urine (Salkowski).

In 1873 Salkowski gave taurin obtained from ox bile to dogs, rabbits, and men. Taurin was recovered from the urine of the dogs and the feces of the rabbits. The rabbits weighing 1,500 gm. received by stomach tube a fatal dose of 4-5 gm. of taurin dissolved in 50 cc. of water. The cause of death was not demonstrated at the autopsy. The rabbits showed toxic symptoms, diarrhea appeared, followed by coma and death. Repeated injections of 1 gm. of taurin were given subcutaneously to rabbits. A large percentage of the taurin fed to, or injected subcutaneously, was recovered in the urine as unaltered taurin. As much as 87 per cent was recovered as hyposulphurous acid and taurin: 56 per cent sulphur as sulphurous acid, 20 per cent as hyposulphurous acid, and 24 per cent as neutral forms, principally as taurin. Salkowski himself took 1 gm. of taurin by mouth on July 5, 1872, and 2 gm. more by mouth on July 6, 1872. To another person he gave by mouth 5 gm. of taurin, and on the third day an additional 5 gm. From this man he recovered sulphur in the urine representing 8.730 gm. of the taurin, indicating a loss of about one-eighth of the total given by mouth. On June 11 and 12, 1873, Salkowski took by mouth 10 gm. of taurin in divided doses, without ill effects. Dogs weighing 8 kg. were fed 5 gm.

of taurin and survived. Taurin was eliminated mainly in the urine, and most of it during the first 48 hours. It was more toxic to rabbits than to men and dogs.

Taurin was obtained in large quantities from the abalone (*Haliotis*) by Schmidt and Watson. Ninety-six abalones (74 kg. of muscle) yielded a total of 362 gm. of crystallized taurin. Mendel had previously found taurin in the muscle of the univalve mollusk. Injections were made subcutaneously and intravenously in rabbits and man (Schmidt, Adelung, and Watson). Taurin, 3 gm., in Ringer's solution was given to one man intravenously, then 10 gm. to another subcutaneously, 10 gm. intravenously, and then 10 gm. by mouth. The doses were given 3 days apart. To a third man, 5 gm. were given by mouth. These men exhibited no toxic symptoms of any kind, regardless of the method of injection. Taurin sulphur was recovered from the urine in various amounts: if given by mouth, 59 per cent; subcutaneously, 62 per cent; and intravenously, 72 per cent. The forms of the neutral sulphur and nature of the compounds by which taurin was excreted in the urine were not determined. Rabbits were given large amounts intravenously, with no toxic symptoms.

Macht, Grollman, and Hyndman observed the action of bile acids and their decomposition products on plants and animals. White mice were studied in the circular maze in order to determine the cerebrospinal effects of bile acids. The growth of seedlings of *Lupinus albus* was observed. Sodium salts of glycocholic and taurocholic acid were poisonous for both animal and plant protoplasm. Glycocol and taurin were slightly poisonous for animals and plants, while cholic, hyocholic, and cholidinic acids were very toxic.

Eighty-seven per cent of taurin was eliminated in the urine, according to Feltz and Ritter, 1875. Six grams of taurin were given intravenously to a 7-kg. dog without effect. Most of the taurin was eliminated by way of the kidneys without change, especially when given by mouth.

Röhrig, von Dusch, Koloman Müller, and Frerichs also found taurin nontoxic.

GLYCOCOLL

No toxic effects were observed by Feltz and Ritter after injection of 12 gm. of glycocoll intravenously into a 5-kg. dog. This work has been confirmed by Röhrig. Glycocoll was found very slightly poisonous for both plants and animals by Macht and Grollman. By comparison, cholic acid was very poisonous.

Glycocoll was fed to dogs in amounts of 15 gm. at a time by Schultzen and Nencki. There was an increase in the excretion of urea which corresponded to the amount of glycocoll given. No glycocoll was found in the feces. Therefore, glycocoll taken by mouth was absorbed from the intestinal tract and excreted quantitatively in the urine. These calculations were made on the basis of nitrogen. There was no toxic action.

Röhrig found that glycocoll had no action on the heart of rabbits when injected intravenously.

RÉSUMÉ

The difficulty in comparing the toxicity of whole bile to pure bile salts is because the amount and form of bile salt in whole bile cannot be accurately determined. Equal quantities of bile salts placed in blood serum, whole bile, and water cannot be accounted for by the Pettenkofer test. There are certain substances in bile, such as phospholipids, lecithin, and cholesterol, which, when added to pure bile salts in water solution, markedly diminish the toxicity. Bilirubin has been proved nontoxic. Nothing other than bile salts, in whole normal bile, has been proved toxic. Other substances which may be toxic occur in bile but are in insignificant quantities.

Whole bile, according to Greene and Snell, is more toxic than either of its major constituents. Meltzer and Salant concluded that the toxic effect of bile was not due to the sum of the effects produced by the components. To support this

conclusion, a knowledge of the character and amount of all the constituents of bile is necessary. It will also be necessary for the bile of each species to be tested in order to obtain comparative results. It is impossible, at the present time, to make a direct quantitative test for sodium taurocholate or for the total cholates. Accurate tests of only one constituent of bile, namely, bilirubin, have been made up to the present time. In man the only acids that call for attention are glycocholic and taurocholic, according to Gillert. Although desoxycholic acid, lythocholic acid, and some others are found in man, they occur in quantities too small to cause toxic symptoms. There does not appear to be a definite quantitative way to measure the toxicity of bile chemically. It would appear, from the work of Wieland, that merely calculating the cholic-acid content of the bile would not give the total toxicity of the bile, for the formation of a compound may cause markedly increased or decreased toxicity of the same molecular concentration. This change in toxicity is the result of conjugation.

CHAPTER VII

NONTOXICITY OF BILE PIGMENTS

BILIRUBIN

BILIRUBIN is the principal pigment in bile. It was first isolated by Berzelius in 1840; he called it *cholephyrhrhin* and worked out the chemical formula. *Biliphaenin* was the name applied to it by Simon in 1845; *bilirubin* was the descriptive term used by Stadelcr in 1864; and *cholophaecin* was used by Thudichum in 1868. A notable array of chemists have worked with this pigment. The crystals of bilirubin were identified in an echinococcus cyst of the liver by Virchow in 1847. He noted the similarity of bilirubin crystals to the crystals of hematoidin, thus first associating bilirubin with hemoglobin. Extravasated blood under the skin appears as a "black and blue spot." The conversion of hemoglobin produces variously colored pigments, which give color to the bruise and are probably identical with the bile pigments. Bilirubin crystals have been found in life in the vessels of the new-born with icterus neonatorum, in brain flexes, among the blood cells in pericardial fluid, and in phagocytes, according to Aschoff. These are all bilirubin I, and he believes they are from the erythrocytes hemolyzed at birth.

Bilirubin is present in the normal human blood serum in the proportion of 1 to 50,000, according to van den Bergh. He found the normal bilirubin in human serum to be from 0.3 to 0.5 mg. per 100 cc. The bilirubin content of the serum was examined in 40 normal, healthy laborers by Rowntree, Greene, and Aldrich, who found the minimum to be 0.2 mg. and the maximum to be 1.0 mg. per 100 cc. These were high bilirubin values of hyperbilirubinemia, but without any pathologic condition demonstrable. There is an increase in

serum bilirubin following exercise and in higher altitudes (Verzár, Arvay, Peter, and Scholderer).

The maximum daily output of bilirubin following operation for biliary obstruction is 587 mg. (Walters). This amount includes the washed-out part.¹ The bilirubin output in bile for 24 hours in man is 0.2–0.7 gm.; and for dog 0.108 gm. (Paton), 24 mg. (McMaster). Bilirubin is normally excreted by way of the bile, urine, and egg tract in birds. In man it is normally excreted by way of the bile and rarely by way of perspiration. A linen handkerchief may be colored a saffron by the pigment in the perspiration (Budd). This explains some of the various colors of sweat, and this kind of perspiration might be considered abnormal, but it causes no trouble.

Immediately following an operation the blood bilirubin increases, gradually returning to normal in 7–8 days. The total pigment output per day is fairly constant. When the volume of bile is low, the concentration of the pigment is greater; and when the volume increases, the relative amount of pigment decreases (McMaster).

OTHER PIGMENTS

In 1878 Hammarsten isolated crystalline bilirubin from horse serum. There are several other pigments which cause the golden-yellow color of the serum in the horse, namely, plasmochrome, isolated by Gallerani in 1904; lipochrome, by van den Bergh in 1913; and carotinoid, by Palmer, 1916.

Normal human serum contains four distinct pigments, which give the serum a golden color. The first isolated was lipochrome, by Thudichum in 1869; then carotin, by Salmon; bilirubin, previously; and xanthophylls, by van den Bergh in 1920.

In swine there is neither carotinoid nor chromolipoid pigment. In goats and sheep there are traces. In milk there are

¹ During jaundice there is retention of bilirubin in the tissues; and after release of obstruction the output of pigment in the bile is greater than normal, owing to the removal of this excess pigment.

chromolipoid, carotin, xanthophylls; in adipose tissue, xanthophylls (Palmer).

In human blood the following pigments appear in various amounts; hemoglobin, bilirubin, hydrobilirubin, carotin (van Norden), lutein (Zoja), urobilin, and biliverdin. All of these give color reactions and may interfere with some of the pigment tests.

The foregoing variety of pigments involves the relationship of plant pigments and animal pigments, such as chlorophyll and hemoglobin. Some of the structural formulas are very closely related. There is also a similarity in the reaction to sunlight.

The oöcyanin of egg shell and the uteroverdin of the dog's placenta, according to Lemberg, are identical with hydrobilirubin prepared by the action of ferric chloride on natural bilirubin: bilirubin by autoxidation becomes biliverdin; mesobilirubin, which is violet, oxidized by ferric chloride, becomes green mesobiliverdin. Mesobiliviolin is similar to phycobilins of red alga.

PHYSIOLOGIC BILIRUBINEMIA

The blood serum of the horse is very highly colored with bilirubin; this is a normal bilirubinemia. The dog has no bilirubin in normal blood serum; this is a physiologic abilirubinemia (1973). Icterus neonatorum has been referred to as a physiologic bilirubinemia.

PATHOLOGIC BILIRUBINEMIA

When there is an excess of pigment in the body, the color of the blood serum increases. The excess may be due to a too rapid formation with normal elimination, as in hemolytic icterus, or to normal formation with faulty elimination, as in obstruction. The bilirubin content of the blood in a normal condition varies according to individual differences but remains, ordinarily, fairly constant. When a sufficiently high concentration is reached in the blood serum, the kidney cells

begin to excrete it. The threshold value is lowest in the blood serum, next in the liver, then in the body tissues (particularly the connective tissue), and highest in the kidney. This portal of exit value of the kidney varies greatly in different species of animals. In the dog it is very low; in the horse and rabbit, very high. It varies greatly in different individuals or in the same individual at different times. Affections of the kidney usually decrease the permeability of kidney cells to bilirubin.

Bilirubin may be increased in the blood serum because of obstruction of the outflow of bile, heart weakness, congestion of the liver, or traumatic hemothorax. There is a slight increase in kidney disease, tuberculosis, cachexia due to carcinoma, and in cachexia of inanition. When the concentration of bilirubin in the blood is greater than 1:50,000 the bilirubin passes over into the tissues and urine. One family has been reported in which two girls had a fawn tint of the skin with high bilirubin concentration of the blood serum, averaging about 1:100,000. This condition is called *biliary diabetes*. The kidney threshold value is about 2 mg. per cent. In hemolytic icterus, pernicious anemia, and cirrhotic atrophy of the liver the blood-serum bilirubin may increase to 3-5 mg. per cent (Bauer and Spiegel). The bilirubin content of the blood increases in nephritis to 0.05; in pneumonia, 0.066; in hypertrophic cirrhosis of the liver, 0.143; and in jaundice, 0.3-1.0 gm. per 1,000 cc. (Gilbert and Herscher). According to Forster, the blood serum of man does not contain more than 2-10 mg. per liter.

In obstructive jaundice the maximum degree of bilirubinemia occurs between the first and second week in dogs; and then the bilirubin in the blood gradually decreases, even though the obstruction is complete (1799).

Bilirubinemia occurs in extrauterine pregnancies, fractures, and contusions, with extravasation of blood. It was present in all new-born infants examined, either with or without visible jaundice. The bilirubin may increase after birth if there has been obstetrical trauma. The ordinary hyperbili-

rubinemia, icterus neonatorum, is a physiologic condition, according to Bang.

INTRAVENOUS BILIRUBIN

The first intravenous injection of bilirubin was made by Tarchanoff in 1874. It was injected into the jugular vein in a dog with gallbladder fistula, to determine its fate: whether excreted by way of the urine. Only a trace of bilirubin was found in the urine, but there was a marked increase in the bile bilirubin. Hemoglobin was then found, but there was no bilirubinuria. This work was repeated and confirmed by Vossius in 1879. For historical reasons the work of Frerichs, 1858, is included. He injected the bile pigment² intravenously into dogs.

The work of Feltz and Ritter,³ 1875, has been quoted so much by various writers that it seems desirable to give it here in detail and show the causes for inaccuracies in their conclusions. During the period in which they worked, bilirubin was a "poudre amorphe." The powder was used as "injection de 2 grammes de bilirubine en solution alcaline," in a dog weighing 10 kg.; the second day, "2 gramme de bilirubine"; the third day, "3 gramme"; the fourth day, "4 gramme."

² Frerichs, 1: 97: "The bile-pigment itself, which is obtained by the action of alcohol upon the dried blood, is sometimes amorphous, but at other times it separates in a crystalline form. These crystals consist of short rods, which adhere in rows to one another, and sometimes form radiated crystalline masses."

³ Feltz and Ritter (568, pp. 154 and 155): "Sous le nom de matières colorantes de la bile on comprend un certain nombre de principes dont l'histoire est encore assez mal connue; si quelques-uns peuvent être regardés comme ayant une composition constante, d'autres ne paraissent être que des mélanges en proportion variable de l'un des principes avec quelques-uns des produits de décomposition. La confusion augmente encore, puisque le même corps a reçu des noms très-différents. Nous devons, par suite, entrer dans quelques détails pour que le lecteur sache bien la nature des composés que nous avons injectés.

"La matière colorante principale contenue dans la bile est la bilirubine (synonymie: cholépyrrhine, biliphéine, bilifulvine, hematoïdine?). Cette substance se présente sous forme d'une poudre amorphe, couleur de kermès ou de soufre doré, peu soluble dans l'eau, l'alcool et l'éther; ses vrais dissolvants sont le chloroforme, le sulfure de carbone ou la benzine. Les alcalis dissolvent facilement la bilirubine; cette solution d'un rouge foncé s'altère peu à peu au contact de l'air, et verdit; nous n'avons, par suite, dissous le poids de bilirubine à injecter qu'au moment même des besoins, dans une solution titrée concentrée de soude, que nous étendions au degré

There was no toxic effect except that the temperature increased 1° for 1 hour. The urine contained bilirubin; and the conjunctiva had a subicteric tint, which appeared a few hours after injection. There was obstinate constipation.

The total volume of the solution injected was not given. In the same article they tell of injecting (p. 148) "20 c.c. d'une solution de cholate de sodium contenant 0 gr. 40 d'acide cholatique"; it is assumed that they injected "3 gramme," by weight, of the "bilirubine" powder in alkaline solution, the volume of which is not given. The amount of powder used for each of four injections was 2, 2, 3, and 4 gm. in one dog and 0.7, 0.9, 1.4, and 1.8 gm. in a second dog.

This would be an extremely large quantity of bilirubin if it were chemically pure. This amount could be obtained only from a very large quantity of ox gallstone, and at the present time the cost is about \$150 per gram for the crystalline, pure bilirubin. As Feltz and Ritter do not give the method of preparation or the source of their "bilirubine," we must assume that they were not working with pure bilirubin.

Bilirubin dissolved in a little soda solution and injected

convenable, par l'addition d'eau distillée; une solution trop étendue de soude ne dissout la bilirubine précipitée que très lentement. Nous avons retiré la bilirubine de calculs biliaires que nous possédions en grand nombre; la bile de porc, traitée directement par le chloroforme, nous a également fourni relativement de grandes quantités de ce produit.

"La bilifuscine, masse poreuse, d'un noir brunâtre brillant, existe dans certains calculs biliaires; elle est soluble dans l'eau, l'éther et le chloroforme; elle est également soluble dans l'alcool; ce caractère permet de la séparer de la bilirubine, quand on extrait cette dernière des calculs biliaires. Sa solution dans les alcalis étendus possède la couleur brune de certaines urines icteriques; elle s'altère également et n'a été préparée pour nos injections qu'au moment des besoins.

"On donne le nom de biliprasine à un composé que l'on retire également des calculs biliaires, en épuisant ces derniers réduits en poudre successivement par l'eau acidulée (qui enlève les sels biliaires), l'éther (qui dissout la cholestérine), le chloroforme (dissolvant de la bilirubine et de la bilifuscine). L'alcool enlève en ce moment une matière verte à laquelle on donne le nom de biliprasine, et laisse un résidu brun qui contient la bilhumine. Ces deux nouvelles matières colorantes (nous pourrions en dire autant de la bilifuscine) ne paraissent pas être des principes immédiats purs; toutes deux se dissolvent dans les alcalis (solutions brunes); il est important, comme pour tous les autres pigments, de ne préparer les solutions destinées à l'injection qu'au moment des besoins."

intravenously into rabbits in doses of 0.05 gm. kills⁴ with certainty,⁵ according to Bouchard with Tapret, 1887. They concluded (230, p. 226) that 5 cg. of bilirubin kills 1 kg. of living matter, and that the lethal dose for a man of weight 60 kg. would be well within 3 gm. The same investigators reported that 5 cc. of water solution of bilirubin for a 1-kg. rabbit will cause death.

Since bilirubin is practically insoluble in water,⁶ the worth of these experiments is seriously questioned. The degree of purity and the method of preparation of the bilirubin used in their experiments were not given. Further investigations led them to conclude that bilirubin is ten times more toxic than bile salts and that bile, filtered with animal charcoal until decolorized, has a greatly reduced toxicity. They concluded that only bile pigment is removed by filtration of bile in this manner and that bile so decolorized is only one-third as toxic as nonfiltered bile.

Greatly diminished specific gravity and toxicity of bile and of pure bile salts, owing to filtering with animal charcoal, have been observed by Horrall. The thoroughly decolorized bile, with its diminished specific gravity, is only about one-third as toxic as whole gallbladder bile. Further, the bile-salt content of the decolorized bile is only one-third of that of gallbladder bile, showing that filtering whole gallbladder bile through animal charcoal removes not only the pigment but a large amount of bile salts. Some of these bile salts can be recovered, however, by repeated washings of the charcoal with distilled water; but unless the filtrate is now boiled to reduce its volume, the percentage in the bile filtrate is very greatly reduced.

The tissues play a protective role, according to Bouchard, consuming and transforming the minute quantities of bile

⁴ This probably is an instance where death was caused by the alkali.

⁵ "Mit Sicherheit."

⁶ Bilirubin is insoluble in water; soluble in warm chloroform; more soluble in alcohol; very slightly in benzene, ether, amyl alcohol, or glycerol. It is soluble in dilute alkalis (Mathews [1216]).

which have been absorbed, after penetrating the general circulation. "They [the tissues] fix the bilirubin." Bile in its entirety passes from the liver into the blood from the biliary cells to the blood vessels. Bile freed from coloring matter loses part of its toxicity; therefore, when the tissues take up the pigment, they remove some of the toxic substance from the circulation; at the same time, bile salts escape by way of the kidneys or are "consumed in the blood." If all bile secreted in 8 hours were suddenly introduced into the blood, it would produce "fatal nervous effect" (question of thrombosis and embolism). But if introduced slowly, nervous accidents are averted. In black jaundice⁷ the absorption is slow and not poisonous, while in green jaundice the absorption is poisonous.

With all the conclusions Bouchard came to, he did not give a single reference to the method of the action of the bile pigment on the tissues. He did show, however, how bile salts act deleteriously on various tissues.

Bilirubin obtained from ox gallstones and injected intravenously into rabbits in quantities of 0.1-0.004 gm., dissolved in sodium carbonate solution, causes death, according to Plaesterer in 1890. Necropsy revealed blood in the urine and in the intestinal canal and a thrombosis of a very high degree of the gut vessels.

This result is probably an example of intravital coagulation of the blood from strong alkali solution given intravenously, followed by embolism and thrombosis of the mesenteric vessels or simple thrombosis of the same vessels. The present writer has observed coagulation within the veins following rapid injection of a 5 per cent sodium carbonate solu-

⁷ Black jaundice (old terminology) is a jaundice of long duration in which the pigment is slowly deposited in the skin, which gradually turns very dark, so that the person appears like a dark mulatto after a duration of many months. It may be a dissociated jaundice in which the pigment is retained and the bile acids excreted normally. Green jaundice is caused by a sudden pigmentation, which may be due to biliverdin showing through a clear skin.

"Experience shows us that the intense form of jaundice, viz. black jaundice, does not kill precisely because the coloring matter, which is ten times more poisonous than the bile salts, becomes fixed. . . . The fibers of the connective tissue are being incessantly colored" (Bouchard [222] in 1864)

tion. Death was due to the alkali rather than to the bilirubin.

Investigation of the toxicity of fistula bile of dogs on rabbits was made by Lugli in 1896. The slow-injection method was used, continuing until death resulted. The toxic coefficient of fistula bile was determined, and then that of the same bile decolorized with charcoal. The specific gravity of the fistula bile was 1.018 and required 26.2 cc. per kilogram of body weight to kill the rabbit; the rest of the experiments gave similar results. The same bile, decolorized and with a specific gravity of 1.010, requires 83 cc. to cause death; another specimen of fistula bile, which had an original specific gravity of 1.017, when decolorized had a specific gravity of 1.009 and needed 85.8 cc. to kill; a third, with a specific gravity of 1.014 with pigment removed, had a specific gravity of 1.005 and required 129.4 cc. for a fatal dose. Lugli concluded that bile is very toxic and that decolorized bile is much less toxic. He reasoned that the pigment contains 60–75 per cent of the toxicity of the bile.⁸

Lugli did not work with pure pigment. His conclusions were drawn from the old prevalent idea that animal charcoal, used as a filter, removes only pigment from the bile. His tables show definitely that the specific gravity is decreased 40–70 per cent by filtering and that the volume of the decolorized bile required to cause death increases from three to four times the original volume. The charcoal removes much toxic bile salts and little nontoxic bile pigments.

Intravenous injections of 0.07 gm. of bilirubin were given to 108 different individuals by Eilbott in 1927. In 6 of the first 30 cases injected, there was a slight reaction. This bilirubin solution had been made up several hours before injection. When a change in the color of this solution was ob-

⁸ Lugli (1143, p. 381): "Die Entfärbung der Galle durch Thierkohle hat eine wesentliche Herabsetzung ihrer Toxicität zur Folge. Die entfärbte Galle ist viermal weniger giftig als die nicht entfärbte. . . . Von den Bestandtheilen der Galle ist das Bilirubin der giftigste. Dies ergibt sich daraus, dass die Entfärbung die Giftigkeit am stärksten herabsetzt sowie directe Versuche mit alkalischer Lösung des reinen Pigments."

served, new solutions were prepared, which were injected immediately after having been made up. In the remaining 78 cases, no toxic reaction of any kind was observed. Bilirubin was being used to test liver function. This nontoxicity was confirmed by von Bergmann.

This method of testing liver function is based on the monopoly of the liver as a bilirubin-eliminating organ and the retention of injected bilirubin as a function test of the liver. Eilbott's bilirubin was made from cattle gallstones after the method of Küster, and was placed in ampules of 0.05 gm. (The normal daily bilirubin elimination for a human is 0.5 gm. [Eppinger].) Bilirubin, 0.07 gm., was added to 10 cc. of a 5 per cent soda solution, warmed to 80° C., and given intravenously. The reactions in the early cases were: temperature increased 1°-2°; and chill, 30 minutes to 1 hour after injection. The second series showed no reactions with freshly prepared solutions. The following findings of bilirubin in the blood were considered normal:

| Milligrams per Cent | |
|----------------------------------|--------------|
| Before injection..... | 0.5 |
| Immediately after injection..... | 2.5 |
| 1 hour later..... | 1.5 |
| 2 hours later..... | 1.0 |
| 3 hours later..... | 0.5 (normal) |

There were 40 normal cases and 68 cases with diseased liver.
Normal retention of bilirubin:

| | PERCENTAGE | |
|-------------------------------|------------|------|
| | Ideal | Real |
| First $\frac{1}{2}$ hour..... | 50 | 43.3 |
| 1 hour..... | 25 | 23.3 |
| 1 $\frac{1}{2}$ hours..... | 12.5 | 13.2 |
| 2 hours..... | 6.3 | 7.4 |
| 2 $\frac{1}{2}$ hours..... | 3.1 | 3.7 |
| 3 hours..... | 1.6 | 1.6 |
| 3 $\frac{1}{2}$ hours..... | 0.8 | 0.83 |
| 4 hours..... | 0.4 | None |

A retention of 10-25 per cent of the bilirubin at the end of 4 hours indicates a damaged liver, but a retention of a greater amount indicates a definitely deficient liver function with liver pathology.

Purified bilirubin was obtained from the Eastman Kodak Company by Greene and Snell (720), 1928, and injected, under local anesthesia, into the saphenous vein of dogs. The period of injection was 1 hour, and the amount was 10-50 mg. for each kilogram of body weight. The bilirubin accumulated in the blood stream: 10 mg. per kilogram with a concentration 2.4 mg. per kilogram per 100 cc. of serum; and 50 mg. per kilogram with a concentration 23.1 mg. per 100 cc. of serum. Bilirubin leaves the blood stream at a much slower rate than the bile acids, and a considerable amount is still present in the blood stream after 4 hours. Injected bile salts can be recovered quantitatively in the bile within 2 hours.

If the rate of excretion were very rapid, the increase of bilirubin content of the blood serum could not have been very high. No satisfactory explanation has yet been offered as to why bilirubin is removed from the blood stream more slowly than the bile acids. One might speculate that the cells of the body have a much greater affinity for bilirubin, as is shown by jaundiced tissues, than for the bile acids, the body tissues thereby retaining the bilirubin much longer than the bile acids. The rate of increase of bile pigment in the blood following intravenous injection would increase much more slowly because the other body tissues are taking it up rapidly. The rate of excretion of bilirubin in the bile would be markedly decreased.

Subcutaneous injections of bilirubin have been made repeatedly. Quincke, before 1899, injected bilirubin in an alkaline solution, 1:100, subcutaneously in dogs, rabbits, and mice and observed no effect except staining of the tissues. He concluded that bilirubin stains only living connective tissue cells and intracellular fibrils, but that in dead tissues it stains muscle, fat, and blood-vessel walls. Bilirubin (manu-

factured by Merck), administered subcutaneously, 0.6 gm. to a rabbit weighing 700 gm., was observed to cause a minimum disturbance. He found the salts more poisonous than the bile pigments.

Bilirubin has been fed to various animals. Naunyn introduced bilirubin, isolated from gallstones, into rabbits, 0.1 gm. in a weak soda solution, by way of the stomach and by way of a fistula of the small intestine into the gastrointestinal tract, and concluded that bilirubin has no effect on bile or bile pigments in the urine. No mention of toxic symptoms was made. The purity of his product is questionable, since he did his work in 1868.⁹

Pure bilirubin in quantities of 100 mg. was fed by mouth to dogs by McMaster and Elman. It was also intubed into the duodenum. An increase in hepatic bile was observed, but there were no bad effects. Eight dogs with biliary fistulas of various types were used, the dogs being otherwise normal. Crystalline bilirubin was prepared from dog fistula bile. Bilirubin 100 mg. was dissolved in 30 cc. of water with the aid of 1 cc. of 20 per cent sodium hydroxide. This was fed to some dogs, and instilled directly into the duodenum in others. The fistula bile was tested for bile pigments, bile salts, and

⁹ Naunyn (1355, pp. 432-33): "Einem kleinen muntern Kaninchen werden p.p.o. 1 Gram. aus Gallensteinen dargestellten Bilirubins in etwa 10 c.c. ganz verdünnter Sodalösung aufgelöst in der beschriebenen Weise in den Dünndarm injicirt. Das Thier ist sogleich nach der Operation völlig munter, frisst und hüpf umher.

"Während der Nacht entleert 20 c.c. eines neutralen Urins, sehr deutlich Gallenfarbstoff-Reaction, Mittags 2 Uhr. 5 c.c. Urin abgedrückt, sehr deutliche Gallenfarbstoff-Reaction.

"Einem kraftigen grauen Kaninchen am 22.4 0.1 gram. Bilirubin in 5 c.c. ganz schwacher Sodalösung gelöst in den Darm injicirt.

"Der abgedrückte Urin zeigt sehr deutliche Gallenfarbstoff-Reaction.

"Nur noch undeutliche Gallenfarbstoff-Reaction.

"Kaninchen befindet sich übrigens fortdauernd wohl; nach 14 Tagen wird dasselbe bei einem andern Versuche getödtet. Keine Spur von Peritonitis. Die Stelle der Injection in den Darm nicht mehr zu erkennen. Die angelegte Unterbindungs schlinge findet sich nicht mehr am Darne vor.

"Es steht nach diesen Versuchen der Annahme, dass auch unter normalen Verhältnissen nicht nur gallensäure Salze, sondern auch Gallenfarbstoffe aus dem Darmkanal ins Blut aufgenommen werden, nichts entgegen."

urobilin. Bile pigment was absorbed from the intestine. Bilirubin fed or instilled caused a greatly increased output of bile pigment. The feeding of bile salts caused the total quantity of bile to be increased and the output of bile salts to be increased, but no increase was noted in bilirubin output. Urobilin fed or instilled caused an excess of urobilin to appear in the bile. An enterohepatic circulation of bile pigment and urobilin was thus demonstrated (McMaster and Elman).

Bilirubin is not absorbed from the intestine by the portal system, and only in small amounts by way of the lymphatics, according to Blankenhorn. He used an ingenious device, making the portal vein accessible for needle puncture through a hollow silver tube. In the same animal he made a biliary fistula by using the "altercursive intubation" of Rous and McMaster, and intubed the thoracic duct. The jugular blood, portal-vein blood, lymph from the thoracic duct, breast lymph, and mesenteric lymph were tested for bilirubin and urobilin. Fasting dogs were fed 20 mg. "pure" bilirubin dissolved in lard. He found that bilirubin, as such, is not absorbed from the intestine by way of the portal-vein in healthy animals, but that bilirubin may be absorbed from the intestine by the lymphatics in minute amounts. Urobilin, however, is reabsorbed from the intestine by way of the portal vein and lymphatics.

Bilirubin, 0.5-10.0 mg., given by mouth produces no toxic effects (Verzár and Zih). Red blood cells and the hemoglobin are increased. Three milligrams given intravenously or by stomach tube to rabbits cause no toxic effects.

INTRALYMPHATIC INJECTION OF BILIRUBIN

Sodium carbonate solutions of bilirubin, 0.004-0.008 mg., were injected into the dorsal lymph sac of frogs by Plaesterer (1481) in 1890, who observed malaise and death.

This work was repeated by Horrall, who used a very weak sodium hydroxide solution. There were no toxic symptoms, and all 12 frogs lived. When a strong carbonate was used, the

frogs died. Sodium carbonate solution was the toxic substance.

EFFECT OF BILIRUBIN ON ISOLATED HEART

Tests of the action of bilirubin on an isolated frog's heart were made by De Bruin (435, 436), in 1889, who found the bilirubin slightly more toxic than sodium taurocholate or sodium glycocholate. In other articles he declares that bilirubin is four to five times more poisonous than bile salts. His last report relates his giving bilirubin intravenously to rabbits in quantities varying from 0.025 to 0.103 gm. per kilogram and finding it toxic. He thought that bilirubin acts principally on the central nervous system and causes convulsions, decrease of blood pressure, fall in pulse rate, jaupneic breathing, increased salivation, and obstipation.

The following extract is from a previously published work of the present writer (852): "The bilirubin was prepared from beef gallstones by a modification of the method of Orndorff and Teeple. The purity of the bilirubin was determined by the spectrophotometric, chemical, and microscopic methods. The bilirubin with which this work was done was of a very high degree of purity and is the same chemical substance as that found in the blood serums of humans and dogs with jaundice and also of that found in normal blood.

"Then twenty-five milligrams of heparin per kilogram of weight of the dog were dissolved in ten cubic centimeters of physiologic salt solution and injected intravenously. This amount of heparin was found sufficient to prevent clotting during the entire experiment.

"The bilirubin was dissolved in various solutions such as sodium carbonate one per cent, sodium hydroxide one per cent, human serum, and dog serum. The solutions were warmed to the temperature of the blood and poured into the reservoir or injected into the rubber tubing on the venous side by means of a syringe and needle.

"Bilirubin was put into the blood in nine dogs with heart-lung preparations. The concentrations varied but reached a

maximum of 2.2 grams per liter. A larger amount could not be used because the quantity of sodium carbonate necessary to dissolve it would become so great that the increase in the blood alkalinity would itself affect the heart. The quantity of sodium carbonate added to the blood in these experiments when tested by itself in the control experiments did not affect the heart. There were slight variations in the pulse rate corresponding to the usual variations in the control heart-lung preparations. The blood pressure did not change in any instance. The fat about the heart and also the lungs became deeply colored, and on allowing the blood cells to separate from the serum the latter had a deep orange appearance.

"For comparison and to see that the heart would react as in the intravenous method, sodium glycocholate 0.662 per cent caused immediate fall in blood pressure, irregular heart, cessation of activity, with acute dilatation of the whole heart.

"Sodium cholate 0.47 per cent caused irregular heart action and fall in blood pressure.

"Whole gallbladder bile, 5 cc. in 210 cc. blood, caused irregular heart with greatly increased amplitude of beat. Atropine then caused slowing of the rate and adrenalin had very slight effect, while a second injection of bile caused a marked increase in amplitude of beat, also increase of the rate. This was soon followed by cessation of heart action. What appeared at first to be the stimulating action of bile, quickly paralyzed the heart.

"The hearts in these heart-lung preparations of dogs did not demonstrate any action of bilirubin, either as a stimulant or as a depressant. The same preparations and similar preparations showed definite effects from whole gallbladder bile, sodium glycocholate, and sodium cholate. The toxic portion of the bile (cholate radical) caused a fall in the blood pressure, diminution in the heart rate, increased amplitude of beat followed by decreased amplitude, irregular rhythm, and acute dilatation of the auricles and ventricles.

"*Conclusion:*—Bilirubin has no effect on the heart."

TESTS FOR BILIRUBIN

There have been many tests for bilirubin, such as Gmelin's color reaction, Maly's test, Ehrlich's diazo reaction, and Jolles' test. These tests are not sufficiently sensitive for the detection of very minute quantities. The modification of Ehrlich's diazo reaction by van den Bergh gave an extremely sensitive qualitative and quantitative test. For his experimental work van den Bergh used "chemisch reinen Bilirubins" (Schuchardt¹⁰). He found the direct reaction in cases with gallstones, catarrhal icterus, or cirrhosis of the liver. Pure bilirubin gives a direct reaction with serum. Another test which is much more sensitive is the photospectrometric test. The technic is extremely difficult, and the instrument used is very expensive. Pure bilirubin in the blood stream does not give a prompt direct reaction, but fresh bile in the serum does. Bilirubin obtained in pure state direct from gallstones does not give a direct reaction (Davies and Dodds). Van den Bergh thinks there is a difference in the composition of the bilirubin found in gallstones and that found in the blood stream.

The physical characteristics of the coloring of bile were analyzed by Wit, who found that the basic gels decolorize bile completely but that the acid gels bind only a small quantity of the coloring matter. Animal charcoal, which is amphoteric, decolorizes best. Bile salts inhibit the absorption greatly, but with the addition of a small amount of acid the decolorization is completed quickly; if protein and acid are added, the color disappears more slowly. He concluded that bilirubin in the blood is dibasic, partly dissolved in the blood plasma and partly bound to the proteins.

The technic of the van den Bergh test is rather simple. The determination of the bilirubin in the blood is a chemical problem with diagnostic importance. The change in the amount of bilirubin in the blood, whether it is increasing or decreasing, indicates the course of the disease and suggests the man-

¹⁰ Manufacturer.

agement. The relation of this test to disease is discussed under the appropriate heading "Icterus."

DISCUSSION

The discussion concerning the toxicity of bilirubin and also the relative toxicity of bilirubin and the bile salts may be summed up in the following manner. Most of the conclusions were arrived at indirectly, and very few workers used chemically pure bilirubin. King and Stewart (1005), 1909, said that "the cost precluded" its use; so they used logic instead. A whole array of investigators arrived at conclusions that bilirubin is toxic and also that bilirubin is more toxic than the bile acids, namely, Bouchard, De Bruin, Lugli, Frerichs, Plaesterer, King and Stewart, Prévost and Binet, and Bowler. On the other hand, there are those who concluded that bilirubin is either nontoxic or relatively much less toxic than bile acids. A few of these investigators worked with chemically pure bilirubin, while many used fairly pure products. The following found that bilirubin is harmless or relatively much less toxic than bile acids: Röhrig, Legg, Feltz and Ritter, von Dusch, Bickel, Rywosch, Leyden, Greene, Eilbott, Quincke, Stadelmann, Still, Horrall and Carlson, and Horrall.

RÉSUMÉ

In 1880 Legg (1082, p. 221) said: "To sum up, it may be stated that the bile pigments are physiologically inert."

In 1928 Horrall and Carlson (856) declared: "Bilirubin is non-toxic."

Erroneous idea of detoxification of bilirubin.—It has been proved conclusively that bilirubin is nontoxic. The idea that calcium bilirubinate¹¹ is nontoxic probably came from the known combination of bilirubin and calcium found in ox gallstones and also in very rare instances in human gallstones.

An article by King and Stewart (1005), which appeared in

¹¹ "Combinée avec le calcium, elle forme une masse vert foncé, à reflets métalliques, le bilirubinate de calcium entre dans la constitution d'une variété importante de calculs biliaires" (1592, p. 44).

1909, is frequently cited. They determined that the lethal dose of pig bile given intravenously to dogs was 36 cc. They then treated pig bile with 5 per cent calcium lactate and filtered it. The filtrate had lost its toxicity, but the alcohol solution of the precipitate was toxic. "These experiments prove that the toxic elements have been removed from the bile by the addition of a calcium salt" (p. 680). "The only explanation which suggested itself to us was that the pigment had lost its toxicity by its union with calcium" (p. 681). No chemical analysis of any of these substances was made. King and Stewart did not work with bilirubin because the "cost precluded." They arrived at their conclusions indirectly on assumptions: the first, that calcium lactate, added to bile, precipitates all bilirubin and only bilirubin; and second, that the intravenous injection of alcoholic solutions is harmless in regard to the alcohol. "The calcium is given up mainly by the bone, to neutralize the toxic bile pigments circulating in the blood and tissues" (King, Bigelow, and Pearce [1904, p. 177].)

This is another erroneous assumption; the evidence is lacking. Horrall and Deninger attempted repeatedly to isolate bile pigments from various biles, according to the method given by King and Stewart. They always obtained a heavy precipitate, which the chemical analysis showed to contain proteins, bile salts, calcium soaps, and a trace of pigment. The assumption that bilirubin in the blood stream in jaundice is the cause of the toxic symptoms has been widespread. There is no direct experimental evidence in favor of it.

Calcium has been administered in various forms, intravenously and orally, presumably to detoxify bilirubin. The lack of available calcium in obstructive jaundice seems definite to Bowler, but he is noncommittal on the question of bile pigment or bile salts as the toxic agent. The blood-calcium total in jaundiced animals is normal (Bowler and Walters). Nontoxic bilirubin is now being injected intravenously to test liver function.

VARIOUS FORMS OF BILE PIGMENTS

Biliverdin is derived from bilirubin by oxidation. It occurs naturally in the bile of herbivores and the blood of cold-blooded animals. It is found in the intestinal tract, and at times in the urine in jaundice.

Biliverdin (Merck¹²) has no effect on the blood and heart, according to Rywosch, 1660. Biliverdin, of unstated purity, was used by King and Stewart.

Biliprasin is a hydration and oxidation product of bilirubin. It occurs in biliary calculi in man and cattle, in the urine in jaundice, and in the placenta of the bitch (Etti).

Bilifuscin is a hydration product of bilirubin and has been found in human gallstones.

Impure *bilifuscin* and *bilihumin* were each injected intravenously into dogs in 4-gm. doses dissolved in weak alkali. *Biliprasin* in 10-gm. dosage dissolved in weak alkali was given intravenously to a dog. There was no toxic effect; and these injections had the same effect as bilirubin injections, according to Feltz and Ritter (568)

The value of these investigations is open to question. So far as the present writer is able to ascertain, none of these pigments has been isolated in chemically pure form in sufficient quantities for experimental work. He was unable to find a method for their preparation; nor were they obtainable. The methods given are for qualitative work only. When these products are examined spectroscopically, the solutions are shown to contain a mixture of several bile pigments.

The beautiful coloring of egg shells is, in most birds, due to bile pigments. In some birds, crystalline bile pigments are excreted in the droppings. The picturesque coloring of the shells of mollusks is due also to these pigments (Krukenberg).

UROBILIN

While examining urine and bile, Jâffe discovered an unusual spectroscopic band; and since the substance which produced it was in both urine and bile, he named it *urobilin*. He

later demonstrated this same substance in normal stools. Urobilin is derived from bilirubin by reduction or from urobilinogen by oxidation in vitro. The usual reduction product of bilirubin is urobilinogen, found in normal feces and in bile; sometimes there are traces of it in normal urine. Normal dog bile contains urobilin and urobilinogen (Fischler), and swine bile contains a greater quantity of urobilinogen (Welzel and Weltmann); but in human bile there is a very scant amount of urobilinogen. In disease the liver urobilin is removed from the blood in larger quantities by the kidney, thus decreasing the enterohepatic circulation of urobilin (Elman and McMaster).

Urobilin was found in the blood serum in fatal cases of pneumonia by Wilbur and Addis. In polycythemia the urobilin is very low in the stool and very high in the urine. Liver damage by alcohol causes large amounts of bilirubin to be excreted in the urine. In lymphatic leukemia the urine contains no urobilin, and the stool very little. In obstructive jaundice there is no urobilin in the urine, while in malaria it is increased in the urine and stool. The theory of the pigment cycle is: Hemoglobin→bilirubin→urobilinogen→urobilin→bilirubin→hemoglobin. Part of the urobilin is excreted in the urine and feces, and part is destroyed; all of it cannot be accounted for in the urine or stool. The test for urobilin is by spectroscopic examination; it produces a fluorescence in the color tests.

There is an increase of urobilin in the urine in infections such as erysipelas, pneumonia, and typhoid fever. In leprosy and in mild forms of pulmonary tuberculosis there is no increase of urobilin in the urine. Royer believes that a knowledge of the amount of urobilin in the blood, urine, and feces is important for the purpose of diagnosis and treatment.

The bilirubin output in bile in 24 hours is 0.3–0.4 gm. (Eppinger), and the urobilin output in the feces is 0.15–0.2 gm. (Neubauer). Therefore, there is a retention of 0.15–0.2 gm. Presumably, this latter amount is absorbed as urobilin. The normal urine excretes 20–30 mg. per day (Adler). A

greater portion of this output is during the digestive period (Lepehne).

When the intestine is free from bile containing bilirubin (that is, a few days following complete obstruction of the common duct), there is a complete disappearance of urobilin and urobilinogen from the urine, the feces, and the bile. If a small quantity of bile containing bilirubin is fed to a dog after such disappearance of the pigments, urobilin again appears in the urine, fistula bile, and feces, indicating that it is necessary for the bilirubin to appear in the intestine before there is any urobilin in the bile. When jaundice has become extensive, urobilin again appears in the bile, urine, and feces. This small amount of urobilin is probably derived from the secretion of a strongly icteric mucous membrane of the intestine (1241). Blankenhorn tested the blood of 128 different unselected men and found urobilin in all but 2 cases. The average was 0.28 mg. per 100 cc. In nephritis, malaria, pneumonia, and tuberculosis with fever the highest value reached was 33.0 mg. The blood of one patient with complete intestinal acholia was clearly negative. This suggests that the origin of urobilin is from the intestinal tract.

Pure urobilin (519), when introduced into the intestine, is absorbed (1241). Purified urobilin, 100–500 mg., dissolved in 50 cc. of 1 per cent solution of ammonium hydroxide and neutralized, was administered to dogs by stomach tube. There were no toxic effects from the feeding of this pigment to dogs. Urobilin was absorbed from the intestine; and dogs which had previously been urobilin-free again showed urobilin in the bile, urine, and feces. The enterohepatic circulation of urobilin has apparently been proved. The use of urobilin in the animal economy is certainly a matter of conjecture at the present time (1242).

RÉSUMÉ

There is no evidence that urobilin is toxic. It appears to be purely an excretion product. Its reabsorption is of no known value.

CHAPTER VIII

TOXICITY OF OTHER CONSTITUENTS OF BILE

CHOLESTEROL¹

CHOLESTEROL was the first substance discovered in bile. Conradi found it in 1775, but Chevreul named it in 1825. Its insolubility causes difficulty in getting it in a suitable solution for intravenous injection. It is entirely insoluble in water and salt solutions (either hot or cold), alcohol, dilute acids, and caustic alkalies but is soluble in hot alcohol, ether, chloroform, some oils and fats, and bile salts. Bile is capable of dissolving solid pieces of cholesterol (Naunyn).

Normal location.—Cholesterol is found normally in the body tissues. Some tissues—such as the brain, nerves, kidney, liver, eggs, and glands—are particularly rich in cholesterol. According to Bouchard, traces are found in all the body tissues. The cholesterol content of the bile varies from 0.5 per cent to 5 per cent (Schafer). Six to 7 gm. of cholesterol are excreted in the bile of man in 24 hours (Roger). The amount excreted varies considerably, and this variation is most noticeable on a rich cholesterol (brain) diet. This type of diet has been criticized as causing an overloading of the system with cholesterol (Whipple). But a bone-mash diet gives an increased cholesterol feeding of 200 mg. per day and causes an increase in the normal output of from 30 mg. per 24 hours to 55–84 mg. It has been suggested that these variations are due to gallbladder and bile-duct secretions. McMaster, in the foregoing experiment, used intubation of the hepatic duct to eliminate this factor.

¹ *Cholesterol* is preferred, as this name refers to the secondary alcohol group; other spellings are: *cholesterine* and *cholesterin*. The name itself implies solid bile.

The work of Jankau has been frequently referred to in the literature on bile. He gave cholesterol in oils or fats by way of the stomach, intestine, and subcutaneously to rabbits and dogs with bile fistula. He could not, according to his test, alter the cholesterol in the blood or output in the bile. McMaster objected to these conclusions on the basis of their testing small specimen of bile rather than a 24-hour specimen. Stadelmann stated that there is no evidence in any instance of cholesterol having an enterohepatic circulation. More recent work tends to support the cycle theory. Cholesterol in food of dogs is absorbed from the intestines, and the amount of cholesterol in the bile following such absorption is increased. Cholesterol in the food of rabbits is likewise absorbed and finds its way into the blood, where it causes an increase in cholesterol esters and free cholesterol. Dog's feces contain unchanged bile cholesterol (1216). The enterohepatic circulation for cholesterol has not been definitely accepted, by all, as proved.

In the recent work of Dostal and Andrews with man and dogs having biliary fistula, cholesterol was found, in the fistula bile, to be independent of diet, oral administration of cholesterol, and oral administration of bile acids.

A quantitative increase in excretion from the blood can be caused in normal rabbits by intravenous injection of cholic and desoxycholic acids, according to the work of Yonemura and Fujihara.

There is no adequate test for cholesterol. Of the several tests employed, some are rather sensitive but are too complicated and not specific. The digitonin test seems to be used most. The objection to this test is that the green color is ever changing during the reading and becomes yellow in 30 minutes.

The normal exit for cholesterol is by way of the bile. Traces are found in the urine. Cholesterol is found in the normal blood serum, 0.09 parts per 1,000 (Becquerel and Rodi); in whole blood, 0.44-0.75. The white blood cells con-

tain four to five times the amount of cholesterol in the red blood cells. The amount in the serum and erythrocytes varies considerably in different animals.

Abnormal locations.—The abnormal locations of cholesterol are: in gallstones in values of 20–90 per cent, almost pure crystals, atheromatous abscesses (Röhrig), arcus senilis, xanthoma, old infarcts, cholesteatomata, and caseous tuberculous lesions (Hewlett).

Variations of cholesterol in the blood stream are associated with physiologic variations and disease. In gestation there is an increase to 2.0–2.45 parts per 1,000; in severe infections with increased temperature, a decrease to 0.5; in chronic nephritis, 15.0; and in diabetes, 270.0 (Frugoni). In jaundice there is usually a marked retention, with a maximum of 8.0.

Flint, in 1862, found much more *cholesterin* in the brain, blood, and bile than in any other parts of the body. He reasoned that the blood receives its cholesterol from the brain and that it passes out through the bile, where it is a purely “excrementitious product.” Much more cholesterol was found in the internal jugular blood, 1.545 parts per 1,000; femoral, 1.28; carotid, 0.967. Therefore, the jugular vein brings the cholesterol from the brain. The muscles of the legs were examined and found to contain no cholesterol, but it was found in the nerves. Blood in the portal vein of dogs contained 1.009 parts per 1,000; in hepatic vein, 0.964; arterial blood, 1.257. The arterial blood gains 23.307 per cent cholesterol in passing through the brain and loses 23.309 per cent in passing through the liver. Bile contains a large quantity of cholesterol, which is, in turn, excreted in the feces as *stercorin*. He concluded that, when there is failure to excrete cholesterol, it is retained in the blood stream and “acts as a poison,” and that the nervous disturbances which are associated with jaundice are due to the accumulation of cholesterol in the blood, which hinder the action of the brain.

The role of cholesterol in icterus was observed by Billandot and Matthieu and by Rosztoczy. The former tied the com-

mon duct in dogs and found pigment in the Kupffer cells in the liver and cholesterolemia when cholesterol was injected. In human obstructive jaundice he also observed pigment in the Kupffer cells and cholesterolemia. Rosztoczy studied the blood, bile, urine, and various organs from normal rabbits and found more free than etherized cholesterol. Following ligation of the common duct, the free cholesterol in the blood and organs was increased; the etherized cholesterol in the organs was decreased, but the etherized cholesterol in the blood was increased. Nevertheless, the total cholesterol was decreased. He concluded that there is an increased destruction of red blood cells which results in the release of large amounts of cholesterol.

Action of cholesterol.—We have some evidence that cholesterol inhibits the toxicity of bile acids and also that it is protective, as it greatly increases the resistance of the red blood cells. Very likely, other factors will be brought to light by further research.

The cholesterol content of the blood increases four or five times its normal value in high-grade bile stasis. Isaac thought he found a parallelism between the cholesterol and bilirubin content of the blood. But McMaster, with very careful and refined technic, concluded that there is no parallelism. Bile pigment remained constant, and cholesterol varied, in 24-hour specimen.

Protective role.—It has been shown that cholesterol inhibits the hemolytic power of a number of substances, particularly the soaps. But Bayer found that the hemolytic action of bile salts is not influenced by cholesterol in vitro.

Pure cholesterol, mixed with bile or bile salts, causes some diminution in the toxic effects of the bile acids. Intraperitoneal and intravenous injections of the mixture likewise somewhat inhibits the toxic action, according to Horrall.

A new role has been assigned to cholesterol by Mazzeo. Rabbits had been given cholesterol for 10 days in succession. Then toxin from culture of *Bacillus dysenteriae* (Shiga-

Kruse bacillus) in varying doses, "d.m.l.—c.c. 0.15," was given to the same rabbits. Protection up to and including 0.60 cc. was afforded by the cholesterol. That protection was effective for five times the minimum lethal dose. In the second experiment rabbits were given a mixture by inoculation. This mixture consisted of cholesterol in saturated ether solution and the toxin of dysentery. Protection up to twenty-five times the minimal lethal dose was afforded. In the third part of the experiment he found that cholesterol given by mouth also afforded some protection but not quite so much as when given by inoculation. The mechanism was not explained, except that cholesterol inhibits toxin of *B. dysenteriae* and assumes a protective role.

Cholesterol, 0.001–0.003 per cent in Ringer's solution, was applied directly to the heart muscle of a frog at room temperature by Danielewsky (422). The solution caused a stimulation. Atropine, muscarine, and curare do not prevent the action of cholesterol. This work should be repeated.

Intravenous action.—In 1863, 8 cc. of cholesterol in saturated soap solution was injected into a rabbit's jugular vein by Röhrig. This injection had no effect on the heart action, as determined by listening to the heart with a stethoscope. This work was repeated by Pagès, who injected cholesterol in soap solution intravenously in a dog and obtained negative results. In the course of 16 days, 2.57 gm. of cholesterol was injected into one dog. In some of the experiments ether was used as the solvent. Koloman Müller reviewed the literature and found that in bile neither the salts nor cholesterol could cause cerebral symptoms and that neither could cause cholemic intoxication. He concluded that cholesterol is toxic, on the basis of experiments made with an emulsion of cholesterol, glycerin, and soap solution, containing 0.45 mg. (8 cc.), which was injected intravenously into 9 dogs, causing coma and death in 56 hours. He inferred that the nervous symptoms are similar to those seen in jaundice and are due to hypercholesterolemia.

Cholesterol dissolved in oil of almonds, making a 5.0 per cent solution, was injected intravenously into cats by Chomjakow (2018, cited). Either death occurred immediately from the infarction of the pulmonary artery or the animal survived without any unfavorable symptoms. Enough cholesterol was added to a 3 per cent solution of stearin soap to make a 0.5 per cent solution. Daily intravenous injections into dogs of from 5 to 45 mg. of cholesterol did not cause any toxic symptoms (von Krusenstern).

Cholesterol in *Nouvelle Solution* was injected into a dog in quantities of 0.025 gm. by Feltz and Ritter in 1875. The injection was repeated six to eight times within a few days, more than 1.0 gm of cholesterol having been injected in a dog without adverse symptoms. They thought that emboli were formed, however, if a large amount of the solid particles in the suspension got into the blood stream. The following is an outline of the experiments of Feltz and Ritter (568, p. 162). Dogs were injected intravenously with *cholesterin* 1 gm. dissolved in 10 cc. of ether; the rate of injection was 1 cc. in 5 minutes, causing death. Emboli were found which contained cholesterol crystals in the smaller vessels in the lungs. They also injected *Nouvelle Solution*, which is composed of

| | | |
|--------------------------|------------------------|----------|
| { "Savon amygdalin"..... | Almond soap | } 30 cc. |
| { "Alcool"..... | Alcohol | |
| { "Ether"..... | Ether | |
| { "Cholesterine"..... | Cholesterol, 0.025 gm. | |

When the foregoing solution was warmed, it dissolved a certain quantity of "cholesterine," which remained in suspension after the liquid was cold. Thirty cubic centimeters of the foregoing liquid were injected at one time, introducing a total of from 0.80 to 1.0 gm. of cholesterol into the blood stream. The following conclusions were drawn: Cholesterol of itself is not toxic; cholesterol accumulates in the blood because it is not excreted; when beyond this maximum solubility in blood, it causes crystallization and emboli. This type of injection was criticized by Bouchard in 1887, who pointed out that

soap and water or "potash" mediums would of themselves kill. Control injections of the same menstruum without the cholesterol were not used. Cholesterolemia, induced experimentally by various processes, is too questionable to be considered seriously. Cholesterol in atheromatous abscesses which were wide open were found at autopsy in the aortic wall of old people. The almost pure cholesterol content of these abscesses amounted to several grams, and there was no indication of poisoning. Cholesterol dissolved in glycerol causes toxic symptoms; but Stadelmann (1824) in 1896 attributed these to the emulsion, surmising that the injection of the suspension causes emboli. Fasiani injected slowly 1.75 gm. of cholesterol in 175 cc. suspension without producing any poisonous effects.

Since the work of King and Stewart has been referred to so frequently by various writers, it should be noted here. The lethal dose of pig bile given intravenously to dogs had been determined at about 36 cc. Then an ether extract of the same bile was made; 0.16 parts of cholesterol per 100 cc. of pig bile were dissolved in alcohol, made up to the same volume as the bile, and then likewise injected intravenously. The lethal dose of this alcohol solution^a of cholesterol was the same as for whole bile; also the same as the bile from which the cholesterol had been removed. They concluded that 0.025-0.176 gm. of cholesterol is lethal.

Subcutaneous.—Cholesterol, 0.5 gm., was dissolved in equal amounts (2 cc.) of *Ricinus-solvin* (castor oil?) and water and injected subcutaneously into a dog by Rywosch. *Solvin* itself is nonpoisonous. No ill effects were observed.

In xanthelasma one finds constantly an increase in blood cholesterol to about 5-6 mg. per cubic centimeter (5 parts per 1,000) (Roger). The normal is 1.7-2.95 mg. per cubic centimeter (Mathews).

Cholesterol is also interesting because of its association with gallstone formation and its intimate chemical relation to

^a Alcohol injection may have caused the death.

bile acids (Wieland). Almost pure cholesterol (98 per cent) gallstones are frequently found in man. They cause no toxic symptoms. The action of cholesterol on the liver is unknown.

RÉSUMÉ

There is no positive evidence that cholesterol is toxic.

LECITHIN

In man, lecithin occurs in gallbladder bile 1.33–29.75 per cent in the alcohol-soluble solids in bile; in fistula bile, 2.54–15.5 (Mathews). Bile salts dissolve 80 per cent of their weight of lecithin. No method has yet been found to separate lecithin from bile (Long and Gephart). The phospholipins in bile are combined with the bile salts at least in part, and neither can be completely separated from the other (Mathews).

Two grams of lecithin were injected into the vein of a dog by Fasiani without producing any poisonous symptoms. Lecithin inhibited the hemolytic action of bile salts, according to Bayer; but in the blood stream the quantity is never sufficient to be of any practical value. Opposing this view, Danielewsky found that lecithin acts as an outstanding stimulating agent on the heart muscle in quantities of 0.001–0.005 per cent solution.

A commercial product of lecithin (Armour³) was repurified in the writer's laboratory. This white crystalline lecithin was then used for the experiments. The bile-salt solution, sodium cholate and ordinary sodium glycocholate, was mixed with this lecithin, making a saturated solution. This solution was injected intravenously and also intraperitoneally into dogs. The toxicity of the bile was slightly reduced.

CEREBRIN

Cerebrin occurs in bile in very small quantities. It inhibits the action of bile salts on the erythrocytes in vitro (Bayer [127]), but probably has no effect in vivo because it occurs in

³ Manufacturer.

infinitely small amounts. Further experiments are necessary to elucidate the role of these lipoids in the bile in normal animals and then to determine their toxicity, if any, under pathologic conditions. Bile constitutes a channel of exit for sterols, phospholipins, and cerebrin. Much research is necessary to determine whether they are pure excretions or of some value in the biliary fluid; very little has been done with them under normal or diseased condition.⁴

MUCIN AND PSEUDO-MUCIN

A mucin-like substance is added to the bile as it leaves the liver, and serves as a protection for the biliary passages and gallbladder. It makes up about 10 per cent of the total solids (Legg); in gallbladder bile, 2 per cent (von Gorup-Besanez) or 3 per cent (Frerichs). Much more is found in gallbladder bile than can be accounted for by the ordinary gallbladder concentration. This particular mucin is different chemically from that secreted elsewhere. The mucin-like substance in the gallbladder is not a true mucin but a phosphoprotein (Hammarsten), which yields no sugar on hydrolysis, as does true mucin (Mathews). A small amount of true mucin may be present in human bile.

OTHER SUBSTANCES

Bile contains a large number of other substances. Extensive lists have been compiled which show marked variations in the constituents, both qualitative and quantitative. The analyses for different species of animals reveal that bile contains many substances not common to the bile of all species. Even within the species, bile in the normal animal varies considerably. Bile contains not only the substances previously mentioned but also a large variety of other organic and inorganic substances. Many abnormal substances are excreted in the bile, such as bacteria, toxins, metallic salts, and dyes. Many substances occur in very small quantities, and under

⁴ Editorial, *JAMA*, 88:1322, 1927.

normal conditions should not modify the toxicity of bile. Under conditions of extensive metallic poisoning, the toxicity of bile is probably increased. For a list of bile constituents, see the chapter so titled.

An attempt has been made to discuss the most evident substances rather than deal with an almost inexhaustible and yet scarcely known list of bile constituents.

"White bile."—In some cases the coloring matter in bile is deficient and does not have its usual bitterness, and the lining of the bile passages is colorless (Budd in 1852).

The finding of white bile at an operation indicates a fatal outcome; Ritter, Judd and Lyons, Rous and McMaster, and Hanot concluded the term itself is a misnomer. The writer was fortunate enough to obtain white bile in two dogs with ligature of the common duct of several weeks' duration. Intravenous injection in dogs, and intraperitoneal in mice, of this so-called "white bile" did not produce any toxic symptoms.

Many colors of bile have been observed in various animals. Practically all of these variations in color are due to changes in the type or quantity of bile pigment, which is nontoxic. Pigment is absent from white bile. Pigment, cholesterol, and cholates were absent from white bile (Drury and Rous), as found in dogs which had received a lethal amount of chloroform and lived only 3 days. White bile, obtained at operation from a patient with jaundice, was analyzed by Lake and Patterson. Chemically, there was no mucin protein, bile pigment, bile salts, and cholesterol; but there was 0.862 per cent chlorides calculated as sodium chloride.

Experimental biliary obstruction and also obstructive jaundice in the human do not ordinarily produce white bile. Something other than mere obstruction seems necessary. Clinically, white bile is sometimes found at operation, associated with stricture of the common duct caused by stone or tumor. White bile is rarely found where there is no apparent obstruction; but when found, it seems to be the result

of cholangitis (Judd and Lyons). White bile found in a patient with deep icterus usually indicates an inactive liver with a high blood urea and gives an unfavorable prognosis (Drury and Rous). Following chloroform-poisoning of the liver, white bile is secreted (Rous and McMaster). Another kind of bile accumulates above an obstruction of the common duct with nonfunctioning gallbladder. This concentrated stasis bile is replaced by a colorless fluid, which may be derived from the liver parenchyma or the secretory cells in the walls of the duct system. White bile is also formed whenever the liver secretes against a pressure obstacle (McMaster, Broun, and Rous). It is not serious if the obstruction is removed early.

In fundamental liver injury the origin of white bile is unknown. When found by surgeons at the time of operation, the prognosis is grave. Bilirubin, cholesterol, and bile salts are all absent from white bile; and there is very little calcium (Drury). When the common duct is tied, there is a liver-cell disturbance or failure and the secretory function is impaired, as shown by the inability to take up and secrete sodium indigotate.

When white bile was found, the conclusion was usually drawn that there was an acholia. The reason for the white bile is that the obstruction is toward the liver side of the collection of fluid; so the white fluid is generally conceded to be entirely free from bile constituents and is a secretion product of the mucous cells in the bile passage, possibly stimulated by bacteria. In other words, this is a hydrops of the bile duct, or, as Gamberini terms it, chemically a transudate of the bile-duct epithelium and a pathologic product of the glands of the ducts. Liver-cell damage with acholeresis and white bile has been observed following phosphorus poisoning by Fischler, following chronic alcoholism by Brauer, and following long-continued fasting by Petroff. The paracholic theory of white bile was supported by Kausch. He thought that the hepatic cells, because of excess pressure in the bile ducts, direct the bile into the blood stream.

Black bile.—Black bile of tarry consistency has frequently been observed in man (Pauchet, Desplas, Matthieu, Dalsace, and Vottero). It is usually associated with gallstones, and recovery is rapid following cholecystectomy or cholecystotomy.

Rust bile.—Rust-colored bile was supposed by Louis (cited by Budd) to be characteristic of typhoid fever.

Green bile.—Green bile was observed by Kanasaki in a man with cirrhosis of the liver. The blood serum contained 172 Meulengracht units of bilirubin. The bile was a grass green, contained no bacteria, but did contain bile sand. Green bile is normal in many animals.

Pleiochromic bile.—Pleiochromic bile is caused by various toxic substances and various dyes (Lepehne).

CHAPTER IX

CONCENTRATION OF BILE IN THE BLOOD

IN THE older literature, when reference was made to bile in the blood, the interpretation was usually made on the basis of the concentration of color in the serum.

The presence of bile in the blood has long been observed. The pigment colors the blood serum and is easily distinguished by chemical tests, but its presence was formerly thought to be due to disease. Recent work has indicated that bile pigments are formed by hemoglobin, transported by the blood to the liver and there removed to be excreted in the bile. Its concentration in the blood is variable, according to the efficiency of elimination. Certainly some bile pigment is present in the normal human blood.

The theory that bile acids are present in the blood has provoked an immense amount of research. Investigators have devised a great variety of tests to determine the existence of bile salts in the blood. The absence of a specific test for cholic acid has prevented the establishment of satisfactory proof of their presence in normal blood serum. They may, however, be present and transported, as the bile pigments are, for selective removal by the liver. This can be determined only when an extremely delicate specific test has been perfected. There is insufficient evidence to prove that bile salts are produced only in the liver. From recent work it must be conceded that when the liver is efficient, cholic acid and taurin, when administered quantitatively to the animal, are readily excreted in the bile quantitatively as taurocholic acid; but the site of their conjugation has not been determined.

In regard to the concentration of bile in the blood, the concern is principally with the amount of bilirubin and bile salts. The quantity of other substances, such as cholesterol

and lecithin, are important but have received very little consideration from the point of view of the study of bile.

CONCENTRATION OF BILIRUBIN

A large number of tests for bilirubin have been developed. The Gmelin nitric acid color test is qualitative. The Salkowski test is also based on an oxidation reaction but is more complicated. The reaction determined by Gilbert and Herscher is satisfactory for a minimum test of 1:50,000 of bilirubin, that is, 0.02 gm. of bilirubin per liter. The lower limit of sensitiveness rules out this test. Ehrlich's diazo reaction depends on a color development by azobilirubin. It is sensitive to 0.001 gm. of bilirubin per liter. This color test cannot be read for 24-48 hours and is attended by too many laboratory errors. The van den Bergh reaction is based on the diazo reactions, the direct and the indirect. This reaction requires only a short time and is sensitive to less than 2 mg. per liter. This sensitiveness approaches the physiologic variation of bilirubin in the blood, and even hypobilirubinemia.

The bilirubin content of the blood serum in man, according to van den Bergh, normally varies from 1:1,000,000 to 1:400,000, which in terms of units is 0.2-0.5 as physiologically normal. In obstructive jaundice in the dog, Snell, Greene, and Rowntree observed 30.8 mg. per 100 cc. of blood serum. In obstructive jaundice the bilirubin in human serum is 71.6 mg. (highest value) per cent, twenty-five times the normal maximal value (Grave). The normal human bilirubin serum, 1:500,000 or 1:600,000, may increase to 1:50,000 or 1:60,000 before any sign of jaundice appears in the skin, urine, or feces (Barrow).

The average normal bilirubin in the blood serum is 0.3-0.5 mg. Judd considered values in the blood of 0.5-1.0 mg. to be normal and found that jaundice appears when 5.0-6.0 mg. are present. The bilirubin content of the normal blood varies considerably according to individual differences, but ordina-

rily remains fairly constant, according to Bauer and Spiegel, with a normal variation of 1.2–2.6 mg.

The spectroscopic test is much more sensitive than the van den Bergh test but requires a specially trained laboratory worker to perform it successfully.

CONCENTRATION OF BILE ACIDS

Since the toxic constituents of bile are the bile salts, it is extremely important to know their quantity in the blood. Many tests have been devised for this purpose. It is necessary to use a chemical method, but there is no specific quantitative test for bile acids or salts. A great number of tests have been devised and then rejected because of numerous complications. The Pettenkofer reaction, with its many modifications, has been used most since its discovery in 1844. The problem has been to eliminate the complicating substances from the blood and other fluids so that a fair test can be made. But the processes developed by a large number of researchers are complicated, and the probability of modifying the bile acids or diminishing them during the test is exceedingly great. Perhaps the best modification up to the present time is that of Aldrich and Bledsoe. However, that test for bile salts is not to be compared with the sensitiveness of the spectroscopic tests for the bile pigment. It must be remembered that no modification of the Pettenkofer test is specific for bile acids. Walker, at Oxford University, has recently shown that cholesteryl oleate in the alcoholic extract of normal blood gives a positive Pettenkofer reaction. The following substances, in addition to bile salts, also give a positive Pettenkofer reaction: Thudichum (1926, p. 121) lists oleic acid, lecithin, myelin, spingosin, and cerebroside; Mylius (1943, p. 495) lists eight substances: isopropylalcohol, isobutylalcohol, allylalcohol, trimethylcarbinol, dimethylethylcarbinol, amylalcohol, "Oelsäure," and petroleum; Udranszky lists forty substances, including the following: omichmyloxyd, uroxanthin, uroglacin, urrhodin, urohematin, uroeryth-

rin, uromelanin, omicholsäure, urochrom, urobilin, bilirubin, hydrobilirubin, indirubin, and indoxyl; and Tashiro and Mills add phospholipids, cholesteryl oleate, phenols (many), aromatic bases, and oleic acid.

The Pettenkofer reaction is ordinarily sensitive to 2 gm. of bile salts per liter. There is no test at the present time, Walker believes, adequate to prove the presence of bile salts in normal blood. He bases this statement on the tests made by using ox and sheep blood, to which he added known quantities of bile salts; he found that the tests did not account for the total quantity of bile acids that had been added.

Many modifications of the Pettenkofer test have been tried, but for one reason or another they are not universally used. The quantitative spectroscopic method, sensitive to 0.1 gm. per liter (Gilbert), and the stalagmometric method of measuring superficial tension are too complicated for general use.

The bile-salt content of the normal blood varies from 3 to 6 mg. for each 100 cc. of blood, according to the Aldrich modification of the Pettenkofer reaction (Aldrich and Bledsoe). The comparison was made with glycocholic acid. Experimental obstructive jaundice in the dog shows a test as high as 16.3 mg. per cent; following intravenous injection of bile acids, 75.0 mg. per cent. Only in intense icterus are bile acids found in the blood; the highest, 0.1 gm. in a liter (100 mg. per cent). In man in obstructive jaundice the acids reach 16.7 mg. per cent, according to Aldrich and Bledsoe. Bile salts in normal human blood are present in amounts of 0.025 mg. of bile salt per 100 cc. of blood; in icteric patients, 2.0–8.0 mg. (Jenke and Steinberg).

Bile acids are eliminated from the blood at different rates, as shown by the work of Snell, Greene, and Rowntree. In normal animals, following intravenous injection, when the blood is tested by the Aldrich-Pettenkofer reaction the blood is found to return to normal within 1 hour; with common duct obstruction the bile acid content of the blood is still high

after 2 hours and remains higher than normal for several hours. However, there appears to be no evidence of an accumulation by injecting every second or third day (Snell, Greene, and Rowntree). In common duct obstruction with the gallbladder present, Mann and his co-workers found that the bile acids increase markedly the first 2 or 3 days, reach the maximum by the second or third week, and gradually diminish to normal about the fiftieth day following obstruction, remaining at a steady level thereafter, with only slight fluctuations. The highest concentration of bile acids is in obstructive jaundice, 30.8 mg. per 100 cc. of blood.

It is generally conceded that bile salts and pigment under normal conditions are rapidly removed from the blood stream and secreted in the bile. Greene and Snell have shown that bile salts are absorbed from the intestinal tract, since they are found in greater quantity in the portal blood than in the peripheral blood.

A reciprocal relation has been observed between Pettenkofer positive substances in the blood and the blood sugar; when the "blood salts" rise, the blood sugar falls, and vice versa (Tashiro and Schmidt, Tietz and Goldblatt). This peculiar relation has also been shown microscopically in the liver: the more bile in the liver cells the less glycogen, and vice versa (Saadi-Nazim and Usuelli). This phenomenon will be discussed under jaundice.

DISSOCIATED JAUNDICE

The French school, headed by Brulé, 1922, and followed by Lemierre, Garban, Weill, Lordat, Widai, and Abrami, has described dissociated jaundice. Either bile salts or bilirubin may be present in large quantities in the blood stream, to the exclusion of the other. Thus, the bile salts or bile pigments either are not produced in the same proportion, are not excreted but are retained disproportionately, or one is reabsorbed and the other rejected normally. Hoover and Blankenhorn and many others do not agree entirely with the views of the French school as to the actual pathology back of

these variations, and others find no bile salts in the blood or urine in *ictère dissocié* (Lemierre and Brulé). Brulé suggests that the dissociation occurs as a differential retention when the hepatic cells become suddenly impermeable to the pigments, causing their retention in the blood, the bile salts being excreted through the liver in the normal manner. Obstruction of the bile capillaries would not result in the selective retention of some one constituent in bile.

In 1931 Tashiro (1893) said that bile salts had not yet been isolated from normal blood. He thought that the methods of proving the presence of these salts in the blood are inaccurate and that, as the methods are improved so as to exclude other Pettenkofer positive substances, the more difficult it will be to show that bile salts are in normal blood. There are "blood salts" which give a positive Pettenkofer test, but these salts do not react like cholic acid. If there is any bile salt in normal blood, it must be desoxycholic acid or compounds very similar to it. The positive Pettenkofer substances normally found in the blood are the greatest in the dog, next in man, then in the horse and rabbit. The technic of the Pettenkofer test (Tashiro, Schmidt, and Tietz) has been perfected to such an extent that cholic acid can be detected in amounts of 0.0027 per cent.

RÉSUMÉ

A number of difficulties are encountered in making the tests for bile salts in the blood, either whole blood or serum. The various bile acids have different physical and chemical properties. The compound or the conjugated bile acids have different reactions from free cholic acid. No one has ever been able quantitatively to separate bile acids from lecithin.

When a specific test for cholates in the blood is discovered which is as sensitive as the spectrophotometric test is for bilirubin, the whole conception of jaundice may have to be reconstructed. The liver is the excretory organ for bilirubin, which, in part at least, is formed elsewhere.

May not the conjugated cholates be products of metabolism of all the cells of the body?

CHAPTER X

THE EFFECT OF BILE ON THE BLOOD CELLS

ACTION OF BILE ON THE ERYTHROCYTES

DESTRUCTIVE ACTION

THE erythrocytes are destroyed by bile, as was observed by Portal in 1813, Hünefeld in 1840, and then by von Dusch in 1854. The disintegration took place as von Dusch made the examination with the microscope. Hünefeld observed this action with the bile of man, ox, dog, cat, bird, and frog, upon the red cells of man, pig, and frog. The action of these different biles on the various red cells was the same, with the exception of the action of bile on the frog's blood corpuscles, in which the nuclei remained unchanged for a longer time but finally broke up into granules, which later disintegrated. His direct observations showed, under the microscope, the disappearance of the red cell when it came in contact with bile, the destruction being so complete that a solution of iodine could not bring ghosts into view.

These observations were applied to the interpretation of jaundice by Gubler in 1858, as reported by Dreyfus-Brisac, his student, who said that, when an extreme amount of blood is destroyed and the liver is unable to eliminate it sufficiently, the colored material accumulates in the blood, causing a discoloration of the tissues. This destruction of the red cells causes an anemia, which can be determined by an analysis of the blood; accompanying the anemia, bile usually appears in the urine. The isolation of bile acids from the blood in biliary obstruction and following intravenous injection and a diminution in the number of red cells, according to tests made by Kühne in 1858, led him to assume that the decrease is caused by bile. Following the injection of bile or bile acids intravenously, he observed the appearance of bile pigments in the

urine and concluded that bile causes hemolysis. The injection into the jugular vein of a dog of 15 cc. of carefully filtered bile obtained from the gallbladder fistula of a dog was followed in 24 hours by dark, icteric urine, which contained, chemically, bile acids and bile pigments. A saturated solution of 5 cc. of sodium glycocholate in 10 cc. water produced in the 17-hour urine albumin, bile pigment, and bile acids. Bile salts were prepared by precipitation of an alcoholic solution of ox gall with ether, freed of pigment and taurocholic acid and crystallized. Cholic acid was obtained by cooking sodium glycocholate for 36 hours with potash, separating with ether, and crystallizing. Sodium glycocholate, 6 per cent solution, or a saturated solution of cholic acid was injected into 7 dogs, causing all to show bile acid and bile pigment in the urine. Death occurred when the injection was made too rapidly. The blood contained bile acids in 24 hours after ligation of the common duct of dogs. Sodium benzoate, 1 gm., was then given; and the urine was found to contain no conjugated bile acids but did contain unconjugated cholic acid. The feces contained no bile acids and no bile pigment.¹

Hemolysis of hemoglobinuria, according to Hoppe-Seyler, 1862, and Huppert, 1864, is caused by intravenous injection of large quantities of bile. Naunyn, 1868, observed that bile acids caused hemolysis and thought that a similar cause might be the logical factor in hematogenous icterus.

Fresh ox bile, filtered or unfiltered, when mixed with blood of the same animal, according to von Dusch, 1854, causes hemolysis. Taurin has no effect, but sodium glycocholate

¹ Kühne (1034, p. 340): "Dass der Blutfarbstoff hierbei in Gallenfarbstoff umgewandelt wird und dass den Gallensäuren ein bis jetzt allerdings noch unerklärbarer Einfluss darauf zugeschrieben werden müsse."

P. 355: "Haben wir zur Genüge gezeigt, dass die Gallensäuren, einen constanten Bestandtheil des icterischen Harns ausmachen, so können wir jeder Annahme entbehren, welche das Gegentheil erklären soll, um so mehr, als diese Annahme sich auf Experimente stützt, deren Resultate im wesentlichsten Theile als falsch befunden worden, da auch nach Injectionen gallensäurer Salze im Harn wieder unveränderte Gallensäuren aufgefunden werden. Das Erscheinen des Gallenfarbstoffs kann aber, wie gezeigt wurde, ohne Zwang von der Umwandlung des Blutroths abgeleitet werden."

sodium taurocholate cause destruction of the red cells. Microscopic examination of the contents of the test tube prove that the cells are completely and suddenly extinguished by bile salts. Iodine solution does not stain the cell membrane (ghost), as it does following hemolysis with distilled water. Frog corpuscles are more resistant to bile than ox corpuscles (Kuhne, Simon).

Ox bile and red blood cells were used by Rywosch in 1888 to determine the toxicity of various bile acids. He criticized von Dusch and Kühne for using a noncrystalline, impure sodium glycocholate. It is interesting to note that Rywosch himself could not have used absolutely pure crystalline sodium taurocholate, for it is not made even now in quantities sufficient for animal experimentation. Kühne used 6 per cent sodium glycocholate on frog's red blood cells and observed no solution of the cells, but the hemoglobin was removed. Leyden, 1866, by the same method, had previously found that the cells dissolve if left in the solution a little longer.

Sodium taurocholate is more hemolytic than sodium glycocholate (Feltz and Ritter in 1874); the mode of action of both salts is identical. Both deform, and then actually decompose, the blood cells. Whole bile has the same action as bile salts. The blood of the dog becomes anemic following repeated intravenous injections of small doses of bile, and the blood fats and cholesterol are increased.

Alteration (*altérée*) of the blood is produced by bile salts passing through the circulation, according to Bouchard, first dissolving* the hemoglobin, then breaking up the red blood cells and finally other cells of the body, causing secondary toxic substances to be set free in the blood stream, thereby producing a secondary autointoxication. He assumed that these secondary substances are responsible for most of the intoxication found in icterus.

Hemolysis following intravenous injection of bile salts was observed by Rywosch, Neufeld, and Handel, while a diminu-

* Bouchard (233, p. 780) in 1895: "Enfin, la bile agit aussi sur les divers tissus."

tion of hemoglobin was recorded by Ruffer after intravenous injection of ox bile into rabbits.

Bile salts, according to Neufeld and Handel, are a protoplasmic poison and have a cytotoxic effect, causing hemolysis of red cells, disintegration of white cells, disruption of spermatozoa, hemorrhage, albuminuria, and lysis of protozoa. A diminution of the red-cell count following intravenous injection of ox bile in rabbits was reported by Ruffer, but he also observed a similar diminution in the red-cell count following injection of bile into the peritoneal cavity of experimental animals. In 1896, experiments on fistula dogs were performed by Stadelmann. Large quantities of bile salts, but no greater than the dog would normally receive in bile, were fed; and there was an increase of bilirubin in the bile. This increase, Stadelmann explained, was due to the action of bile salts on the red cells. He pointed out that sodium taurocholate, 1:600, destroys red cells and that the sodium glycocholate, 1:50, has the same action. Therefore, he concluded that sodium taurocholate is about ten times more toxic for red cells than sodium glycocholate. Ox bile, human bile, and the bile of other animals were found, by von Dusch, 1854, to have the same effect on the red cells. But Lüdke in 1906 reported that bile of the various animals differs much as to hemolytic power; this difference was not accounted for by the variation of solid constituents or in any other way. Ox bile and sheep bile injected intravenously into rabbits caused a diminution of red cells and hemoglobin. In vitro, bile hemolyzes and then destroys the red cells. Anemia follows the ligation of the common duct and also occurs in external biliary fistula in dogs, according to Adler and Brehm. Anemia can be prevented in dogs with gallbladder fistula by giving 50 cc. of ox bile twice a day by mouth, according to Seyderhelm and Tammann (1752). The question as to which constituent of bile causes the anemia in biliary fistula is still unsettled. An anemia is found almost constantly in obstructive jaundice, which includes a diminution in the total num-

ber of red cells and hemoglobin in experimental animals and men with jaundice. This is probably a secondary anemia.

PROTECTIVE SUBSTANCES

A remarkable property of the blood, preventing the destruction of red cells by the cholates, was observed by Lüdke. Plasma diminished the action of bile and bile salts in destroying the red cells. There was something in the blood serum making it more protective than a simple physiologic salt solution. It has been suggested that the proteins in the blood stream counteract the action of bile salts. Lüdke's experiments in vitro were made by adding small amounts of blood serum to a suspension of red cells before the addition of bile. The cells of ox, sheep, hog, horse, rabbit, dog, goose, guinea-pig, and goat were used; and either autoserum or heteroserum were found to be protective agents. The bile used to hemolyze the cells was obtained from ox, dog, sheep, pig, and man. The method of procedure was to use a 5 per cent suspension of red cell, 1 cc., and serum, 0.1 cc. and up, to which bile, 0.5 cc., was added. Hemolysis always occurred if the serum had not been added. When a sufficient quantity of the serum had been added, it protected the red cells from the hemolyzing action of the bile.

Hemolysis by bile salts is prevented by plasma, according to the findings of Bayer (127). Lecithin in the blood serum possesses some inhibitory action but not in large enough quantities. Digestion of the serum proteids destroys the protective action. Bile acts on emulsions of lecithin similarly to the lysis of corpuscles. Thus, Bayer (128) concluded that bile salts cause hemolysis by acting on the lecithin in the erythrocytes. This action was explained as due to a physical combination of serum albumin and bile salts, forming a colloid, which protects against the action of the bile on the red cells and on other cells and tissues in the body. In contrast to this, he said that the liver cells have an affinity for bile.

The action of bile on the red cells is attributed to the

combination of lecithin and bile; and, because of this affinity,³ Bayer attributed the nervous symptoms in jaundice to the action of bile on the lecithin in the brain. Distilled water acts on the red cells, causing them to swell; the internal pressure on the cell becomes so great that the cell wall becomes permeable for hemoglobin. But saponin acts on the lipoids of the cell, thus permitting the hemoglobin to escape without the red cell increasing in size. The bile salts cause a chemical disintegration of the lipoid-structure constituents, thus freeing the hemoglobin. The bile salts do not act on the cell wall alone but on all the lipoids throughout the cell.

In obstructive jaundice the erythrocytes have an increased resistance to hypotonic salt solution, but the resistance to saponin is diminished, from which it would appear that the bile acts like a saponin substance on the lipoids in the red cell. The bile in jaundice having already acted, to a certain extent, on the red cell, when only a small amount of saponin is now added the hemolysis is completed.

A dilution of blood serum 1:30 protects against 1 mg. of sodium taurocholate in 1.5 cc. fluid total for red blood cells; the protein in the serum inhibits the hemolysis by bile salts (Sellards). Fresh gallbladder bile from the pig and sodium glycocholate and sodium taurocholate (Eimer and Amend⁴) were tested against washed pig corpuscles and against human corpuscles and serum. Preparations with normal serum showed complete protection against twenty times the animal hemolytic dose and also complete protection against eight times the dose of sodium glycocholate and bile salts required for complete hemolysis.

Bile salts are active hemolytic agents in vitro. Normal serum protects effectively against the hemolytic action of bile. In serum dilutions as high as 1:3,000 a trace of this

³ Lecithin inhibits the action of bile for hemolysis as cholesterol inhibits the action of saponin (as a poison) hemolysis. *Affinität*=chemical affinity. The *Affinität* of liver for bile is that it selects it from the blood stream, that is, it does not remove urea, as the kidney does.

⁴ Chemical manufacturers.

protection still persists. Precipitation of the proteins by heat does not affect this inhibitory property of the serum. The blood serum has a specific action by which it destroys the poisonous effects of the bile salts. It protects the erythrocytes from hemolysis.

The hemolytic action of bile salts is inhibited by blood serum; 0.1 cc. of serum lengthens the time required for the hemolysis of 1 cc. of a 5 per cent suspension of human red cells by 1:1,000 sodium taurocholate from $\frac{1}{2}$ minute to 7 minutes. But, since bile salts do not attain the concentration of 1:1,000 even in intense jaundice, there can be no hemoglobinuria even in the most intense icterus, according to the work of Ponder (1492), who was unable to produce increased inhibitory power of the serum of rabbits to hemolysis by repeated intravenous and subcutaneous injections of sodium taurocholate. This is in accord with Sellards (1741) and Bayer (127) but is not in agreement with Lüdke (1140) and Ruffer and Crendiropoulo (1648).

The action of bile on the blood cells *in vitro* has been demonstrated, but the animal experiments are not yet sufficient to prove a definite action of bile on the cells *in vivo*. The protecting effect of the blood serum is, without doubt, great enough to prevent a considerable amount of bile salts from causing destruction of the red blood cells. The fact that hemoglobinuria is absent in jaundice furthers this belief. The continual presence, however, of bile in the blood over a period of time may cause a harmful result.

Hemolytic sera were occasionally produced by repeated injections of bile. Ruffer and Crendiropoulo observed hemolytic serum in two rabbits following injection of ox bile. Heat completely destroyed these hemolytic properties. Hemosozic powers of serum also have been produced by repeated injections of bile, but in the living animal these properties do not cause appreciable effects.

The bile of sheep, man, rabbit, and horse was used in investigations made by Ruffer and Crendiropoulo. Ox gallblad-

der bile was removed with sterile pipettes. The red blood cells of sheep, man, guinea-pig, and rabbit were washed with physiologic salt solution. Bile dissolved, with unequal rapidity, the corpuscles of animals of the same and other species. Fifteen drops of ox bile dissolved 2 drops of human or bovine blood cells in 5 minutes, but it required 18 hours to dissolve the rabbit's cells. Temperature above 60° C. reduced the hemolytic properties of bile. Filtering with charcoal did not remove all hemolysins, indicating that they were not connected with the bile pigment. Hemolysins were soluble in alcohol and water but insoluble in ether. Ether or chloroform extract of fresh bile had a marked inhibitive (protective) effect (hemosozic) on the hemolytic action of bile.

FRAGILITY OF ERYTHROCYTES

The normal fragility of the red cells varies considerably. The standard tests are for cells washed with salt solution. The cells may all be very fragile, all very resistant, or some very fragile and some very resistant. Since jaundice is dependent on the pigment in the cell, it may be assumed that the more freely it is released, or the more hemolytic the serum, the greater the likelihood for the appearance of icterus. If bile salts in the blood stream cause destruction of the red cells, the weaker cells are destroyed first, leaving the resistant cells in the circulating blood. Thus, in obstructive jaundice, increased resistance of the remaining red cells would be expected. Rusznák and Barát found that, after partial hemolysis with bile salts, the upper boundary of hemolysis increases when tested with hypotonic salt solution; a chemical influence by the bile salts on the osmotic resistance of the red cells causes this increase. The fragility of the red cells in jaundice, tested with varying concentrations of salt solution, definitely decreases, according to Giffin and Sanford. This does not appear to be due to the actual change in the cell wall but is probably due to the previous destruction of the fragile cells, resulting in jaundice; the cells which survived the de-

structive process were being tested. Thus appears the paradoxical increase in the resistance of the red blood cells in jaundice.

The osmotic resistance of the red cells in hemolytic jaundice is markedly decreased, as reported by Richards and Johnson. In obstructive jaundice the resistance of the erythrocytes is increased to hypotonic salt solution. In chronic acholuric jaundice the resistance of the red cells not separated from the plasma is markedly decreased; but, when separated from the plasma, it is more markedly decreased. The normal red cells in plasma and washed red cells have the same resistance. The resistance of the erythrocytes is increased by obstructive jaundice; and the degree of the resistance runs parallel to the bilirubin content of the blood, as determined by Nakajima and Kimura.

If bile salts were to act as saponin on red cells, the general structure of the cell lipoids would be altered and all the cells would become more fragile, owing to the weakened cell.

Jaundice, however, may be of the dissociated type, there being a hemolytic agent other than the bile salts in the blood.

The hemolysis begins in hypotonic salt solution at 0.46 per cent of sodium chloride solution and is complete at 0.36 per cent. These values vary somewhat but are recognized as a standard by Chauffard. The following figures for hemolysis were given by Chabrol:

| | | |
|---------------------------------------|---------------------|-------------|
| Congenital icterus..... | 0.36 complete | 0.62 begins |
| Familial icterus..... | | .66 |
| Chronic splenomegalic anemia of Hayem | Varies considerably | |
| Before splenectomy, cholemia | at times | .68 |
| 1:30,000..... | 0.50 | .78 |
| After splenectomy..... | 0.40 | .58 |
| To minium..... | 0.28 | .44 |
| After crisis, cholemia 1:9,000..... | 0.40 | .58 |
| Icterus of new-born..... | | .52 |
| Hemolytic syphilitic icterus..... | | 0.52-0.70 |

It would be interesting to know the amount of bile salts in the blood in the foregoing experiment and to compare it with

the fragility. There are no known figures on this comparison. The blood bilirubin varies greatly.

SEDIMENTATION

In investigations on sedimentation time, Rosenthal and Blowstein took red blood cells from 60 patients, using the Linzenmeier method of citrated blood, and noted the time when the red blood cells reached the 18-mm. mark. The time for normal blood is 180 minutes. The normal sedimentation rate for man is from 2 to 18 mm. per hour; for woman, 3-29 mm. per hour, which is 5-58 per cent per hour (Burke and Weir). In jaundiced cases the sedimentation time was 80 per cent less than normal. There was no relation to the degree or duration of jaundice or of bile obstruction. The majority of cases with jaundice had an increased sedimentation rate for red blood cells. Hypercholesterinemia (300 mg.) was associated with an increased sedimentation rate. Many jaundiced cases showed marked variations. What underlying factors influence the variations in the sedimentation time have not yet been determined. The sedimentation rate of red cells in vitro with bile salts did not correspond with the sedimentation rate in icteric plasma. Bilirubin has no effect on sedimentation in vitro (Johannes, Vorschütz, Katz, and Radt); bile salts have a marked effect; cholesterol hastens (Kürten), while lecithin inhibits.

OTHER ROLES

Sugars have an inhibitory action on hemolysis by sodium taurocholate, according to Ponder and Yeager, who suggest that the inhibitory effect is due to the increase in the resistance of the cell and also to the depression of the hemolytic effect of the bile salt. Sucrose is most active but does not antagonize the effect of bile on coagulation.

A new role for bilirubin has been suggested by Verzář and Zih. Bilirubin in doses of 0.5-3.0 mg. (and even 25 mg.), given with stomach tube to rabbits, causes an increase of 1,000,000 erythrocytes. The hemoglobin is also increased. They likewise attribute this hematopoietic activity to biliverdin.

If it could be understood how bile throws red blood cells into solution, Bayer thinks rational therapy could be advised in cholemic conditions.

RÉSUMÉ

Bile salts hemolyze erythrocytes *in vitro*, but the evidence is not sufficient to prove actual hemolysis *in vivo* in jaundice.

LEUKOCYTES

Bile has the same destructive effect on white blood cells as on other animal cells. Ameboid movements are inhibited, as observed under the microscope by von Dusch in 1854. The action of bile salts on the white blood cells is similar to the action on the red blood cells: first there is an increased fragility, then a complete destruction of the cells (Rywosch). Liver cells, however, are more resistant to bile salts than the white cells. Ciliated cells from a frog resist for 5-10 minutes a 3 per cent solution of sodium taurocholate. The solution of ameba and infusorians has also been observed.

A variation in the differential count of the white blood cells following injection of ox bile intravenously into rabbits was found by Ruffer and Crendiropoulo. The eosinophiles are markedly decreased, likewise the lymphocytes. The neutrophiles are proportionately increased, the large lymphocytes are slightly increased, and myelocytes make their appearance. The total white count is diminished, but later on it returns to considerably above the normal. This high count lasts for several days, finally returning to normal. A leukocytosis in animals following administration of bile was observed by Leyden in 1866 and by Brown in 1875. Injection of bile into the peritoneal cavity causes the leukocytes in the blood stream to be greatly increased, with a preponderance of polymorphonuclear leukocytes. Subcutaneous injection of bile and bile acids in man and laboratory animals causes a strong leukocytosis similar to that found during digestion (Hari). Bile salts cause lysis of leukocytes *in vitro*; the addi-

tion of homoserum has a marked inhibiting effect (Bayer [129]).

Bile exerts an early definite chemotactic effect on the white cells when injected into the tissues. This is most easily observed when bile is injected subcutaneously, causing large abscesses to develop.

RÉSUMÉ

Leukocytes are dissolved by bile salts in vitro. They are not affected so rapidly or in such dilute concentrations as the red cells.

CHAPTER XI

BLEEDING IN JAUNDICE

OCCURRENCE

HEMORRHAGE in jaundice has been frequently observed. It is seen in acute jaundice but more often in long-continued jaundice with marked pigmentation. Huxham in 1739 wrote about hemorrhagic diathesis in jaundice, saying that it was not uncommon and that the bleeding could not be modified by treatment (1082).

This hemorrhagic condition has also been observed by Budd, Bamberger, and Leyden. Hemorrhage occurs from the mucous membranes more frequently; a cut or injury is often followed by bleeding. Budd surmised that the bile in the blood causes a continuation of the hemorrhage; and Leyden concluded that it is due to the bile acids, which cause the destruction of the middle coat of the arteries.

Hemorrhage following operation has been observed clinically much more frequently in patients with jaundice caused by obstruction of the common bile duct than in those having other forms of jaundice. This becomes a very important clinical condition for surgeons who operate on patients with jaundice. According to Walters (2041), serious postoperative hemorrhage occurred in more than 50 per cent of the cases of obstructive jaundice coming to autopsy. In more than 70 per cent of the cases in which hemorrhage caused death in the presence of obstructive jaundice, the preoperative coagulation time of the blood was more than 9 minutes, according to Walters. Postoperative bleeding caused 15 per cent of all the deaths following operation on the gallbladder and bile ducts; and of all the patients operated on, 1-2 per cent died of cholemic hemorrhage (Petrén in 1925). A question exists as to the relationship of coagulability of the blood and hemorrhage.

Hemorrhagic diathesis occurs in 40 per cent of the cases of icterus, 38 per cent of the cases of latent icterus, and 13 per cent of nonicteric cases. Obstruction of the common duct by malignant tumor with diminishing liver function furnishes the largest number of these cases, according to Soejima.

Purpura and hemorrhage are frequently observed in jaundice. The purpura may cover almost the entire body, or there may be a few patches of capillary bleeding in the skin. Hemorrhage occurs from the nose, intestinal tract, or any mucous membrane. Following intravenous or intraperitoneal injection of bile, bloody stools may appear, and even red cells or hemoglobin may pass in the urine. At autopsy petechiae are frequently observed, and occasionally massive hemorrhage in the gastric and intestinal mucosa, in the lungs and kidneys, and in the peritoneal cavity. The contact of the bile salts here, if made, is by way of the blood stream. Surgeons have observed a marked increase in the coagulation time of the blood and have hesitated to operate when the blood requires longer than 10 minutes to coagulate, because of the great mortality from hemorrhage.

Hemorrhages occur spontaneously in obstructive jaundice. There is injury to the capillary endothelium, causing a solution of the intercellular substance with small spontaneous effusions of blood (Morawitz). Diapedesis and extravasation follow the action of bile on the walls of the blood capillaries. Johnson, Shionoya, and Rowntree found that the bleeding occurs almost entirely from the capillaries, and concluded that jaundice is a purpura. From the large volume of blood, it would seem that bleeding occurs, not from minute capillaries entirely, but also from fair-sized blood vessels.

Direct bleeding from the arterioles was observed in dogs following the injection of ox bile, causing injury to the vessel wall, according to Schmidt (1702). Intravenous injection of bile salts frequently causes bloody intestinal fluid. There is marked hyperemia of the submucosa. Rywosch (1659) explained this as a passive congestion due to heart failure, fol-

lowed by endothelial lysis of the blood vessels by the bile salts.

Vasoconstriction was observed by Rywosch following intravenous injections of large doses of bile and bile salts. In small amounts, bile caused vasodilatation. These phenomena were observed when bile was applied either to the inside or the outside of the blood vessels. Samelson saw a vasoconstriction under the microscope when bile was applied locally. Pulmonary hemorrhages were thought by von Dusch to be due to tearing of the blood capillaries following intravenous injection of bile.

Hemorrhage occurs in various locations following obstruction of the common duct, as observed experimentally. The most common are along the gastrointestinal tract, in the submucosa or serosa. Following intravenous injection of bile and bile salts, petechiae are found at necropsy in the submucosa of the gastrointestinal tract, in the serous membrane of the peritoneal, pleural, and pericardial cavities, throughout the lungs, kidneys, and meninges. The larger the quantity of bile injected, the more extensive is the hemorrhage and the greater the number of bleeding-points. Following intraperitoneal and intrapleural injection of bile, massive hemorrhages occur in the mesentery, and smaller ones in the rest of the peritoneum and in the intestinal canal. At times there is a bloody diarrhea. Blood frequently appears in the vomitus and urine. Hemorrhages are rarely visible in the skin of the dog.

COAGULATION

Since there is a marked tendency for hemorrhage in jaundice, the relation of icterus to the coagulation time and the effect of bile on coagulation should be determined. The coagulability of the blood in 238 normal and jaundiced patients was investigated by Nygaard. The mean coagulation time in normal persons was $3\frac{1}{2}$ minutes; most rapid, 2 minutes; and the slowest, $4\frac{1}{2}$ minutes. In 90 jaundiced patients the mean was 4

minutes; most rapid, $2\frac{1}{2}$ minutes; and the slowest was greater than 9 minutes. In the deaths occurring from hemorrhage in jaundiced patients, the coagulation time was greater than 4 minutes. Some of the jaundiced patients, however, had hemorrhage with a coagulation time of 3 minutes. The increase in coagulation time seemed to predispose to the tendency to bleed and to fatal hemorrhage. Various conditions, such as the time of day and the taking of food, may affect the coagulation time of the blood.

In vitro the coagulation time is increased by 0.5 per cent bile acids. It is doubled when from 0.5 to 1.0 per cent are added to the blood. When a greater amount of bile acids is added, the coagulation is inhibited (Morawitz and Bierich).

The optimum for coagulation with sodium taurocholate and sodium glycocholate is 1:500, and the time is less than normal (Rywosch, 1659). Concentration of these bile salts of 1:250 abolishes coagulation. Samson-Himmelstjerna found sodium glycocholate to be more active in inhibiting coagulation than sodium taurocholate, but Rywosch found the reverse. Schmidt (1702) found that 1 part of bile to 20 parts of blood causes definite inhibition of coagulation. After inhibition has once started, it does not depend quantitatively on more bile. Bile salts give the same result as bile, that is, 0.25 per cent inhibits blood coagulation and 1 per cent prevents coagulation for 1 hour; both cause hemolysis. Petré (1462) found that 0.2 per cent inhibits coagulation in vitro, but Melchior (1258) pointed out that the highest bile-acid content of the blood in icterus is under 0.05 per cent.

If the cause of the diminution of coagulation of the blood is not directly due to the cholate portion, then it is possible that the intensity or duration of the icterus causes damage to the blood or to the blood vessels. The delay in coagulation roughly parallels the degree of jaundice, and that parallels the duration of obstruction. In jaundice of the new-born there is very little, if any, tendency to bleed.

The lowest level of bile acids necessary to produce a

minimal effect on the coagulation in vitro is 0.25 per cent, according to Morawitz and Bierich, or between 0.17 and 0.22 per cent, according to Petrén. The highest level yet found was 80 mg. per cent in a necropsy specimen (Johnson, Shinoya, and Rowntree). Fatal hemorrhage was observed in a patient with nonobstructive jaundice with a Pettenkofer value between 20 and 26. This amount of bile acids, even in vitro, has very little effect (Rowntree, Greene, and Aldrich).

In the study, by Johnson and Rowntree, of extracorporeal thrombosis in rabbits there was an increase in coagulation time of from 3 to 15 minutes, following the continuous intravenous injection of 600–700 mg. of bile salts in solution. The normal coagulation time of rabbit's blood is 6–10 minutes. In jaundice caused by ligation of the common duct after 3–5 days the coagulation time was increased to 10–15 minutes; the thrombi were white and poor in fibrin content. Coagulation time may be increased by bile salts to 3–4 hours. The indirect role of bile acids in the production of delayed coagulation time and cholemic bleeding has not yet been disproved, neither has it been definitely proved that bile acids of themselves actually cause this increased bleeding. In a case with jaundice of 3 weeks' duration, there was an increase in the coagulation time. This was attributed to the inhibition of the formation of thrombin. The blood calcium content and fibrinogen content quantitatively were normal.

It is well known that emboli and thrombosis frequently occur when bile is rapidly injected intravenously. The reverse action is caused by a strong alkali, with destruction of some of the blood elements and immediate coagulation. Just what mechanism is involved is not clear.

There is seldom any risk of postoperative bleeding in icterus until the disease has persisted for 3 or 4 weeks. Hemorrhagic diathesis can persist after high-grade icterus of long standing, even when this has begun to subside or is near disappearing. In vitro addition of bile salts to blood, 0.2 per cent bile salts, slows coagulation time; 0.6 per cent entirely

inhibits coagulation of normal blood (Petrén [1463]). Since there is such a discrepancy in the amount of bile salts necessary to affect the coagulation *in vitro* and the amount of bile salts found in the blood in severe icterus, Petrén concluded that the bile acids have nothing to do with the hemorrhagic diathesis in jaundice.

The method of calculation of bile acids in the blood has so many possible sources of error that it is doubtful whether an exact statement can be made concerning the relation of bile to coagulation. Up to the present time, tests sufficiently sensitive to determine slight changes in cholic acid in the blood have not been discovered. Frequently the statement appears that the bile acids in the blood are normal. The sources of error are so many and so great that this statement is only roughly true. Prévost and Binet found that bile salts 20-26 mg. in the blood stream have a very slight effect on blood coagulation. Minkowski and Naunyn have found bile acids in the blood and the tissues in partial extirpation of the liver in birds; but if the extirpation is total, none accumulate. Partial extirpation would then be similar to clinical jaundice.

Investigation of the other constituents of bile have revealed no coagulation-inhibitory substance (Morawitz and Bierich).

Either the bile acids do not cause the increased coagulation time or the blood may contain some substance or substances which neutralize the toxic action of bile. A decrease of these constituents would thereby result in a delay in the coagulation time of the blood. If the bile acts on these antagonizers, Tashiro and Lee believe a much smaller quantity of bile salts would be necessary to produce the typical delayed coagulation in jaundice. This is an excellent lead for further investigation.

FIBRINOGEN

In obstructive jaundice in dogs, Moss (1321) determined the coagulation time and fibrinogen² content of the blood.

² The normal blood fibrin content in men is 170-340 mg. per 100 cc. of blood; for women, 280-360 (Burke in 1933).

The fibrinogen content of the blood plasma increased immediately following operation. The degree of obstructive jaundice was measured by the pigment content of the blood (icterus index). The fibrinogen content of the blood remained high, somewhat paralleling the icterus index while the coagulation time diminished. The fluctuation in coagulation time was parallel with the degree of icterus, but the coagulation time did not parallel the fibrinogen content of the plasma.

It is doubtful if the icterus index is a satisfactory method of determining the changes in the blood. The determination of the bile salt content of the blood would have been most interesting in these cases.

Morawitz thought that when the fibrin content of the blood is normal but the thrombokinase deficient, the delay in coagulation time might be attributable to delayed formation of fibrin enzyme.

Bile salts interfere with the conversion of fibrinogen into fibrin, delaying or inhibiting the coagulation of the blood, according to Haessler and Stebbins. Bile salts also hinder the action of fibrin ferment, but the addition of calcium salts may paralyze this inhibitory action. Bile salts may prevent the formation of this ferment. Diluting the plasma-bile mixture may cause the slow formation of a clot. Schmidt (1702) concluded that the bile salts, even though present principally as neutral salts in the separating concentrations, have the power to inhibit the action of fibrin ferment and thus produce the bleeding of jaundice.

Blood fibrin in postoperative cases shows a sharp rise, then a gradual return to normal, and after several days maintains a high normal. Coagulation time and fibrin content of the blood have no direct relation to each other in jaundice, according to Foster and Whipple (622).

CALCIUM

A considerable amount of evidence has accumulated which shows that there is no deficiency in the amount of diffusible

calcium or of any other kind of calcium in jaundice (Gunther and Greenberg). No direct proof has established the idea that the calcium in the blood of jaundiced patients is deficient. The injection of calcium into the blood stream only temporarily increases the blood calcium, sometimes modifying the coagulation time of the blood. The intravenous injection of glucose has the same effect on the coagulation time.

In obstructive jaundice with hemorrhage the coagulation time is delayed 8-15 minutes. The coagulation of venous blood is greatly retarded in obstructive jaundice. The total calcium in the blood serum does not vary from the normal following jaundice, as reported by Lee and White, who found the coagulation time in jaundice greatly prolonged. The calcium time in jaundice is also greatly prolonged in animals and remains so until death.

In a dog with obstructive jaundice, Snell, Greene, and Rowntree found the coagulation time to be 8-12 minutes. The normal for a dog is 4-7 minutes. The total calcium of the serum was normal. There was a parallelism between the retention of bile and the prolongation of the coagulation time.

The lethal dose of intravenous calcium in normal dogs is 287 mg. per kilogram of body weight; but in jaundiced dogs, 469 mg. (Bowler and Walters). The blood calcium in normal dogs is 10.3 mg. before and 42.9 mg. after injection; in jaundiced dogs, 10.9 before and 38.7 after. Almost twice as much calcium is required for a lethal dose in the jaundiced dog as in the normal. The blood-serum calcium at the time of death is less in the jaundiced than in the normal dog.

What happens to the excess calcium injected into the jaundiced dog is mere conjecture.

The addition of calcium to jaundiced blood cannot restore the blood to its original coagulability (1894).

PLATELETS

Since platelets are intimately associated with blood coagulation, changes in their appearance under the microscope or

diminution in their count is easily observed. In severe jaundice the platelets are frequently very large and irregular in outline, as seen when stained by cresyl blue, followed by Wright's stain. The platelet count was definitely decreased in some clinical cases with jaundice that have been under the writer's observation. There are very few references in the literature to such alterations. Dill, however, found no change in the platelets in 6 rabbits with ligation of the common duct for 14-33 days.

PROTHROMBIN

A new factor was found by Howell and Holt in 1918 in the coagulation of blood in jaundice. They assigned the term *pro-antithrombin* to this defective factor in jaundice with liver destruction. Then Nygaard in 1932 reported a deficiency of prothrombin in the plasma of patients with obstructive jaundice. This observation was confirmed by Quick, Stanley-Brown, and Bancroft, in 1935. They extended the work and found the coagulation time was still greatly prolonged, even though they added in excess to jaundiced plasma either thromboplastin, or calcium, or both. Then the only other variable was prothrombin, which they found was decreased in the blood of jaundiced patients. The origin of prothrombin is uncertain, but evidence is offered by Quick in 1937 and by Dam that it is related to vitamin K or to avitaminosis.

DISTURBED LIVER FUNCTION

Disturbed liver function has appeared to be the cause of cholemic bleeding through the process of elimination. Because Röhrig in 1863, Ranke in 1871, and Feltz and Ritter in 1872 failed to find bile salts in the blood in sufficient quantities, they concluded that bleeding is due to disturbed liver function. Quincke (1525) thought that the bleeding in jaundice is due to hepatic intoxication. Quincke and Hoppe-Seyler (1526) pointed out that bleeding in jaundice is not due to overloading of the blood with bile acids but is probably due to disturbed liver function by some unknown toxic product.

Cholemic bleeding, hemorrhagic diathesis, was attributed by Morawitz and Bierich to liver destruction or liver alteration, since in these conditions they found blood-vessel damage. The intensity of pigmentation of the blood serum was not an index to the coagulation time. Hirudin and fibrin ferment acted quantitatively; bile did not seem to do so. This view was further supported by the clinical and experimental work of Soejima.

The cholemic tendency to bleed is due not to the abnormal enrichment of the bile acids in the blood but to the effect of a strong functional disturbance of the liver itself, according to Melchior's clinical observations (1258). The coagulation of the blood is accelerated by treatment with abundant calcium and gelatin preparations, or the like.

The normal fibrinogen content of the blood of dogs varies from 62 to 250 mg. per 100 cc. (Wohlgemuth); after extirpation of the liver the fibrinogen content varies from 15.5 to 250. The fibrin ferment varies from 62.5 to 250 (normal 125-250); after extirpation of the liver the variation is from 7.75 to 62.5. The coagulation of the blood with the lowest fibrin-ferment content is considerably delayed. A definite diminution of the fibrinogen and fibrin-ferment content of the blood follows extirpation of the liver; and, where there is a great diminution, the delay in coagulation is prolonged. Cholemic bleeding is due, as a part of this syndrome, not to the icterus but to deep-seated liver damage. It is not in proportion to the degree of jaundice coloring but to the amount of liver damage which causes an altering of the fibrin ferment, hence a "pseudo-hemophilia hepatica."

The absorption and retention of a large quantity of bile salts by the liver itself, according to Petrén (1462), causes functional changes in the liver, which result in a prolongation of the coagulation time. The bile salts themselves cannot be held directly responsible. Liver poisons, such as chloroform, phosphorus, and hydrazine, in small doses, are stimulating and increase the fibrin values. If there is a sufficient injury

of the liver parenchyma by large doses, the fibrin values decrease, according to Foster and Whipple (622); and they concluded that any damage to the liver parenchyma produces a fall in fibrin content and a diminution in the coagulability of the blood, with tendency to hemorrhage. Not only the action of bile, and particularly the bile salts, but also the pathology underlying the jaundice itself, may play a direct role in hemorrhage (Rywosch). Bile does not check coagulation because of its antithrombic action, and has no effect on fibrinogen or calcium; but bile acids, 0.1 per cent, in the blood do check coagulation. Cholemic hemorrhagic diathesis is not caused by icterus but by the functional disturbances in the liver (Soejima).

Since fat necrosis usually precedes and is associated with hemorrhagic necrosis, Bunting and Brown pointed out that there may be a combination of bile and lipase in the fat cells, causing the hemorrhagic condition.

The fibrinogen content of the blood is markedly diminished following injury to the liver, as found experimentally by Whipple. The liver probably plays additional roles in regard to coagulation of the blood, and particularly with a diminution in the coagulation of the blood in jaundice.

The intensity of the icterus does not seem to have any relationship to the bleeding, but jaundice of long duration appears to be more likely to bleed. The tendency to hemorrhage may be in proportion to the amount of liver destruction rather than to the degree of jaundice. Mann and Magath found, in dogs with complete hepatectomy living longer than 11 hours, a delayed coagulation of the blood.

TREATMENT

A case of mechanical obstruction of the common duct of 3½ years' duration was reported by Wangenstein (2051). The blood-coagulation time was 29 minutes; the calcium time, 23 minutes; the prothrombin time was negative after 14 hours; the serum-calcium was 8.67 mg. per 100 cc. Following ad-

ministration of calcium carbonate by mouth and calcium chloride intravenously, the coagulation time was $11\frac{1}{2}$ minutes and the calcium time $9\frac{1}{2}$ minutes. A hypodermic injection of 1.5 cc. of a thromboplastic preparation was given. Sixteen hours later the clotting time was $9\frac{1}{2}$ minutes; calcium time, $6\frac{1}{2}$ minutes; and prothrombin time, 23 minutes. Intravenous whole-blood transfusion was given, and the coagulation time was $8\frac{1}{2}$ minutes; calcium time, 8 minutes.

Few instances do occur in man in which the coagulation of the blood is not modified by calcium chloride administered intravenously. Glucose given intravenously or whole-blood transfusion further improves the coagulation. Calcium does not restore the blood to its original coagulability (Tashiro and Lee). Calcium chloride is not a true detoxifying agent, but it does cause diminution in the coagulation time. The mechanism of the action of the calcium and chloride has yet to be determined; but, since its use does actually cause a diminution in the coagulation time in patients, it cannot be discarded.

Glycerol neutralizes the anticoagulation property of sodium taurocholate. The amount of glycerol required is very great (Tashiro and Lee). Intravenous injection of glucose certainly modifies the coagulation. Galactose, 40 gm. with one-half lemon, in water, given by mouth, decreases the coagulability of the blood within 2 hours (Nygaard). Cholesterol shortens the coagulation time where the bile salt concentration is very small (Tashiro and Mills). Glucose is a good antagonist of sodium taurocholate in blood coagulation (Kobes).

An interesting fact that many investigators have omitted to note is that the tendency to bleed does not occur early in jaundice. This tendency to bleed is first noticed 2 or 3 weeks after the onset of jaundice; and, after it has continued for several weeks, the probability of hemorrhage is greatly increased. Even after the jaundice has diminished, this tendency to bleed persists for some time. As shown by Mann and

his co-workers in obstructive jaundice, the increase of bile salts in the blood stream appears very early; and after 2 or 3 weeks, even though the obstructive jaundice is complete and continues, the bile salts in the blood stream decline to normal, and after 4 weeks remain at practically the original normal level. It is about this time that the tendency to bleed begins, and it continues until it reaches its maximum several weeks after the onset of jaundice. The subject of liver damage in relation to blood coagulation in jaundice is very complex.

The method of preventing hemorrhage and at the same time decreasing the coagulation time has been shown experimentally and clinically to be accomplished by intravenous calcium, intravenous glucose, and blood transfusions. The chemical mechanism of calcium and glucose in preventing hemorrhage has not been determined.

RÉSUMÉ

Undoubtedly, there is a change in the coagulability of the blood in jaundice. The relationship between coagulability of the blood and hemorrhage shows a marked variance on a number of points. There is no definite relation between hemorrhage in jaundice and fibrinogen, calcium, phosphorus, and coagulation time. There is a prothrombin deficiency. The exact cause of hemorrhage in jaundice has not yet been determined.

CHAPTER XII

ACTION OF BILE ON THE NERVOUS SYSTEM

GENERAL EFFECT

THE frequency of occurrence of abnormal mental symptoms in jaundice led to the inference, even in the time of Hippocrates and Galen, that bile had a definite effect on the activities of the brain. To black bile, various symptoms associated with melancholia were attributed. Hippocrates¹ associated malignant jaundice with delirium and convulsions. All the mental symptoms which appeared in persons having jaundice were attributed directly to bile. Certainly many of these symptoms must have been caused by other types of intoxication, as jaundice is only one symptom of a series of processes that are going on.

Catalepsy has been reproduced by Baruk and Camus in the pigeon, cat, mouse, and guinea-pig by subcutaneous injections of neurotrophic bile removed by duodenal tube from a patient with the foregoing nervous disturbance. Somnolence, stupor, hyperkinesis, paralysis, biliary anxiety, and melancholia follow the injection of the appropriate bile. Baruk and Camus were unable to reproduce the symptoms by beef and pork bile cholesterol, bile pigments, and bile salts; so they suggest the possibility that poisons in the bile cause these symptoms.

Convulsions, tetanus, and death of rabbits following intrajugular injections of filtered bile, sodium glycocholate, and sodium taurocholate were observed by von Dusch in 1854.

¹ In *Ad Democritum philos epist*: "Qui ex pituita insaniunt quieti sunt, qui Vero ex bile hi verberant, malefici sunt, neque quiescunt."

In *De morbo sacro*: "Qui ex bile insaniunt clamosi, maligni et minime quieti sunt, semper aliquid intempestiven faciunt."

"Bilis ut plurimum hominum insaniae causa" (822, 3:799).

"Bilis ad caput recurrens delirii causa" (Galen [656, 15:741, 598])

The several symptoms in jaundice were not definitely proved to be the result of bile salts, and he concluded that the cerebral symptoms of icterus occurred only when bile acids or their products appeared in the blood stream with bile pigments. At autopsy he found hemorrhages in the lungs, and the right side of the heart filled with a blood clot. He failed to recognize that the cause of death was thrombosis of the pulmonary artery, and attributed death to the effect of bile on the cerebrum.

The effect of bile on the nervous system in diseases of the liver has been extensively discussed; nevertheless, there had been no experimental evidence until the work of Bouisson, 1841. The discovery of bile acids by Strecker in 1848 was followed with work by a number of investigators: von Dusch, 1854; Kühne, 1859; Frerichs, 1860; Albers, 1862; Röhrig, 1863; Ranke, 1864; and Leyden, 1866.

Nervous symptoms were observed by Bouisson following the intravenous injection of bile, but Frerichs found no remarkable derangements of the nervous or other functions following injection with filtered bile. The injection into a frog of 20 cc. of a 0.5 per cent solution of sodium glycocholate caused general diminution of sensibility in 20 minutes and a complete loss of sensibility in 1 hour (Ranke). Leyden rarely observed convulsions following intrajugular injections of 1 cc. of a 10 per cent solution of sodium glycocholate. Bile salts first caused poisoning of the blood; then the central nervous system was affected as animals gradually lost their sensibility. The reflexes also were decreased, but stimulation of the motor nerve yet called forth action. Bouchard injected a mixture of bile and water, 4-6 cc. per kilogram, intravenously into rabbits. The addition of water prevented the formation of mucous emboli; nevertheless, convulsions and death resulted. When bile was filtered with animal charcoal, it lost two-thirds of the toxicity.

Convulsions, or coma and death, frequently follow cerebral emboli of any sort. Convulsions occur in uremia, eclampsia,

and in anuria, and cannot be considered as pathognomonic of the action of any one particular substance. Bouchard said that jaundiced persons are not affected by bile but by cellular destruction products, and that therefore the nervous system is secondarily affected. As evidence he offered the statement that the urine from a jaundiced person is very toxic and causes convulsions but never causes necrosis, showing that the poison is derived from cellular destruction.

EFFECT OF BILE ON THE BRAIN

A peculiar method of testing the effects of bile on the brain was used by Bickel (172), Biedl and Kraus (177), and Bruno (291). Bickel observed convulsions following subdural applications of bile and concluded that bile irritates the brain. Similarly, Biedl and Kraus (177) observed convulsions following subdural injections of bile. Bile and bile salts were injected through trephined holes in the subdural spaces of rabbits, mice, guinea-pigs, dogs, and frogs. The quantity used varied from a few drops to 1-2 cc. of dilute bile. One cubic centimeter of bile killed a rabbit in 24 hours. First muscle stiffness appeared in the neck and back; then convulsive movements spread over the entire body, as evidence of the poisoning. Other previously observed symptoms of bile toxicity appeared also, such as bradycardia and dyspnea. Controls—such as water, salt solution, morphine, atropine, blood serum, and urine—were injected without any toxic symptoms. Strong acids and alkalies, when injected subdurally, caused convulsions and early death. Strongly jaundiced urine caused the same symptoms of toxicity. Bile salts dissolved in normal urine caused similar symptoms, but bilirubin crystals and bilirubin dissolved in alkaline solution were entirely harmless. Sodium cholate (*Natrium choleinicum* of the German pharmacopoeia), sodium taurocholate (Merck²), and sodium glycocholate (Merck²) were used, and the toxic symptoms of the action of bile on the brain were

² Chemical manufacturer.

observed. Recently Coquelet applied bile to the surface of the brain or injected it into the arachnoid and observed convulsions, prostration, and death. Lichtman injected bile by way of intraspinal and cisternal punctures and found that even minute doses are toxic and that the medullary centers in the cat are very sensitive to bile salts.

Injections of bile into the carotid artery produce toxic symptoms similar to those caused by subdural injections of bile (Löwit). Biedl and Kraus even suggested that, since this method is so sensitive for bile, it may be used for testing quantitatively for bile salts in the urine. This work was repeated by Bruno, who observed convulsions following subdural injection of a comparatively harmless substance, such as methylene blue, intravenous injections of which are practically inert. The same results were obtained by subdural injections of morphine.

A depressant action on the brain was observed by Macht (1154), following injection of bile salts into rats, as shown by the maze-running tests. He used 0.5 mg. per 100 gm. of rat.

Central paralysis, convulsions, tetanus, and coma follow injections of bile into frogs. The method of Meltzer and Salant (1266), however, was an indirect one; they sensitized frogs with strychnine, using a subminimal dose, and then injected 3 cc. of ox bile or 2.0–3.0 cc. of rabbit bile. The bile of some animals predominantly caused coma, while that of others mainly caused tetanus. The heating of the bile reduced the paralyzing effect and increased the tetanic element. Bile from nephrectomized rabbits had a greater tetanic element than bile from the normal rabbit. In an animal completely paralyzed by bile, electrical stimulation of the cord had no effect, but stimulation of the sciatic nerve caused active contractions. Stimulation of the peripheral end of the cut vagus, after intravenous injection of bile, caused a fall in the blood pressure, showing increased irritability. Injection of a lethal dose did not completely inhibit the response of the vagus to stimuli so long as the heart was beating perceptibly,

but finally it caused a standstill of the heart. Vagus inhibition lasted as long as the heart beat. Stimulation of the vagus nerve in an atropinized animal which had been injected intravenously with bile still affected the heart. The entire toxicity was not in the bile salts, according to Meltzer and Salant, because they found the tetanic element was less in bile salts than in whole bile, but added, "We still do not wish to draw final conclusions from our series of experiments with bile salts."

THE EFFECT OF BILE ON NERVES

Bile or sodium glycocholate, 1-2 per cent solutions, applied to nerves causes stimulation, according to Kühne (1035), 1859. Röhrig (1604) found that bile given intravenously to rabbits has an effect even after the vagi are cut. This action was attributed to the laking of the red blood cells, causing defective nutrition, thus weakening the myocardium. He concluded that bile does not affect the vagi or the brain. Bile acts on the nervous system as a stimulator or inhibitor, according to the concentration of the bile salts used (Glur).

Frogs were injected by Ranke (1538) in 1864 with 20 cc. of a 0.5 per cent solution of sodium glycocholate. After 1 hour, stimulation of the cord caused only weak convulsions; 20 minutes after the injection the reflexes were gone; therefore the ganglion apparatus was affected. He concluded that the effect was primarily on the nervous tissue. Leyden, following the injection of bile acids in frogs, stimulated the peripheral end of the sciatic nerve and observed strong reflexes. Stimulation of the central end caused scarcely any movement on the opposite side. The action was on the central nervous system rather than on the nerve muscle.

The activity of bile on the peripheral nerve was tested by Rywosch (1658) by using the sciatic nerve of the frog, with the muscle in salt solution. The bile-acid salt solution in strong concentration plainly affected the conductivity of the nerve in the nerve-muscle preparation. In sparing concentra-

tions of bile salts the conductivity was also affected. He concluded that there is a chemical action of the bile salts on the axis cylinder; that bile affects the motor nerve ending; and that all bile acids affect the nerves but that taurin and glycocoll do not.

The action of bile and bile salts is similar to that of curare poisoning; they retard muscle chronaxia while the nerve chronaxia remains unchanged, according to Lyon-Caen (1151). The methods used by Lyon-Caen were those of Lapique for measuring the modification for the chronaxia of nerve and muscle when acted on by toxic substances. Bile salts act as very rapid poisons. *In vitro* experiments were done with the gastrocnemius muscle-nerve preparation. *In vivo* experiments were done by injecting a limb which had been ligatured at the base to prevent circulation of the bile salts.

The action of bile salts on the neuromuscular function and reflex centers of the cord has been studied by Ries and Still (1576). They gave dogs, rabbits, and cats, under barbital anesthesia, intravenous injections of sodium cholate and sodium dehydrocholate. The conduction through the nerve fibers was not affected by the bile salts; and the irritability of the vagal endings was increased by small doses of bile salts while large doses produced a block.

The direct application of 5 per cent sodium glycocholate to the peripheral nerves of a dog acts as a local anesthetic, but later it acts as an electrical stimulus, causing muscle contraction (Coquelet). The conductivity of the nerve is diminished (Manta). Weak bile raises the excitability, and strong bile inhibits it (Perichanjanj).

Intravenous bile causes a decrease of creatinine in the urine of rabbits, and poisoning of the sympathetic nervous system causes an added decrease; thus Taku concluded that the action of bile is not peripheral but central.

Bile causes an increase in glycogen formation in the liver (Maki), a decrease of the glycemia, lowers the respiratory

quotient, depresses the metabolic rate (Hatakeyama), alters the electrolytic quantity in the tissues and organs, and changes the ion concentration in the blood (Zondek); therefore it acts through the sympathetic nervous system. But with large doses the vegetative nervous system is poisoned; then the bile acids act on the central nervous system.

The theories advanced by various investigators in their attempt to explain the occurrence of nervous symptoms in jaundice may be summed up as follows:

1. Bile salts circulating in the blood (Leyden) (intravenous injections of bile salts will not reproduce the nervous symptoms)
2. Failure of the liver to detoxify the blood normally
 - a) Uremia (Rokitansky)
 - b) Cholesterolemia (Flint)
3. Decomposition of the liver with absorption (Budd)
4. Hemorrhages of the meninges (Monneret)
5. The poison which causes jaundice may also injure the brain

Objections may be found to each of these theories. A combination of any or all of these may cause the symptoms.

Dilatation of the pupils is very often the first indication of the appearance of the nervous phenomena (1082, p. 443). Headache, restlessness, excitation, and later collapse, convulsions, coma, delirium, and even mania may occur. Drowsiness is frequent. Early in jaundice an increased sensibility of the skin occurs, while late in jaundice there is a decreased sensibility.

In simple jaundice the nervous symptoms may last for only a few hours or for a few days. In the majority of cases they last no longer than 48 hours. A depressed condition is common late in jaundice. Mental sluggishness, drowsiness, stupor, and coma occur. These symptoms probably are not due to bile salts but to the general toxic condition of the patient. Metabolic disorders from nonfunctioning or malfunctioning liver are present. It is difficult to prove the direct toxic action of bile here. Nervousness may be present early and may be due to an excess of bile salts in the system. But severe symptoms

which occur late in the disease with jaundice, such as delirium and mania, can hardly be attributed to the toxic action of bile per se. Here, again, too many other conditions must be considered. Jaundice is frequently accompanied by cancer, and in jaundice of long standing there is always great malnutrition.

SEDATIVE ACTION OF BILE

The irritative activity of bile and bile salts is the more noticeable as a result of actual physical motion following injection of bile salts. In jaundice the nervous excitement has been ascribed to bile. These preliminary symptoms are followed, sooner or later, by a general depression. In some cases the stage of excitement does not appear; there is a gradually increasing languor from the beginning, or even just prior to the onset, of jaundice. Melancholia and depression have been observed in jaundice ever since the days of Hippocrates.

Recently Hench (796) has reported 12 cases with various kinds of arthritic pains which subsided with the appearance of jaundice. The mechanism involved is not understood; the action of various bile constituents, the effect of hepatitis, and many other possibilities must be investigated.

Jaundice has been widely observed following the administration of cinchophen for the relief of pain in arthritis and kindred conditions. Frequently, however, the blood serum and urine became icteric. This was generally considered an inconvenient complication; but when cinchophen was discontinued with the appearance of the first sign of jaundice, the outcome was generally favorable and the rheumatic pain subsided.

The effect of bile acids on vague arthritic and similar pains has been investigated recently, but it has been thought advisable to make no published reports until more data are available. Speculation is not warranted on the meager information available at this time. Indiscriminate, promiscuous, and careless use of toxic bile salts may be very detrimental, if not fatal. This is a new field for clinical investigation.

CHAPTER XIII

ACTION OF BILE ON THE HEART AND BLOOD PRESSURE

ACTION OF BILE ON THE HEART

BRADYCARDIA in jaundice is well known. Clinical observations have been made frequently of a slowing of the pulse even to 20 or 30 beats per minute. A diminution of the heart rate to 21 beats per minute in a severe case of icterus was reported by Frerichs before 1863. The early observers naturally attributed the slow heart to the jaundiced condition, and particularly to bile after the early experiments had shown bile and some bile constituents to be poisonous. They found that the pulse frequency gradually diminished with the deepening of jaundice, usually after the first 3 weeks, and then, with the clearing of the jaundice, the pulse frequency gradually increased to normal. In 1863 Landois (1061) and Röhrig (1604) reported the observations of the slowing of the pulse clinically. From then on, such reports were frequently made. In his work published in 1902, MacKenzie (1158), the famous heart specialist, said that he had never observed bradycardia in icterus. Clinically in hemolytic jaundice, a condition with pigment in the blood but no bile acids, bradycardia is never found, according to Chabrol (337, p. 109). Especially in feverless icterus, which is severe, a slow pulse rate is found (Traube). He cited one case in which the pulse rate was 44 beats per minute while sitting still and increased to 76 when walking about the room. He observed, after bile injection, a dicrotic pulse. When this pulse is observed on the sick bed, death is predicted within 36 hours. In the isolated mammal's heart the pulsation is definitely slowed by bile. Bradycardia is the rule in the course of icterus of hepatic origin, according to

Bouillaud (337, cited) in 1864. Tachycardia is more prevalent than bradycardia clinically, according to Greene and Aldrich.

The experimental work began in 1852 with Budge (300), who was the first to describe the action of bile on muscle. Bile brought directly into contact with the heart muscle caused the heart to come to a standstill. This was followed by the work of many investigators, who attempted to determine which constituent of bile was responsible for the cessation of the heart action, namely, von Dusch, 1854; Frerichs, 1856; Städeler, 1856; Kühne, 1858; Neukomm, 1860; Albers, 1862; Hoppe, 1862; Röhrig, 1863; Landois, 1863; Traube, 1864; and Naunyn, 1868. The last observed a slowing of the pulse in a small dog which had been fed 2 gm. of sodium *choleiate* in sausage.

BILE CONSTITUENTS

Various bile constituents have been investigated to determine which are toxic to the heart.

Bilirubin.—The early records of the action of bilirubin on the heart have little scientific value, since the experiments were performed with a pigment of great impurity or with a pigment whose identity had not been established. The procedure in many of the experiments was first to determine the action of whole bile on the heart; then to remove bilirubin from the bile by chemical or mechanical means; and finally to use the depigmented bile on the heart. The manifest error in such work was that other bile constituents were removed with the bilirubin or chemically changed by any agent which would remove bilirubin.

An immense amount of work has been done to determine the action of bilirubin. The findings of investigators who have admittedly been unable to secure pure pigments must be discounted. King and Stewart (1005) found that the "cost precluded" the use of pure bilirubin, but concluded that a lethal dose of bile is smaller when it contains the pigment than when the pigment is removed. They also believe that

calcium or sodium bilirubinate is less toxic than the uncombined bilirubin. This is contrary to the observation on dogs made by Horrall, who found that the addition of calcium to pure bilirubin increases the toxicity. This increase is probably due to the calcium and not to the formation of a calcium bilirubinate. This latter substance could not be demonstrated in the mixture. The older workers who used impure bile pigments, such as Röhrig,¹ concluded that the pigment does not affect the heart. De Bruin, 1889, concluded from tests on the isolated frog's heart that bilirubin is toxic.

The recent work of Horrall (852) was done with extremely pure bilirubin on heart-lung preparation from dogs. Bilirubin was put into the blood of 9 dogs in concentrations varying up to 2.2 gm. per liter of blood. Heart tracings did not show the slightest evidence of toxicity. For further details of this work, see the chapter on bilirubin.

Bile salts.—Pure bile salts have been injected repeatedly into experimental animals and man, and the effect on the heart observed. In small doses there are indications that there may be an actual increase in the heart action (Glur). In larger doses Röhrig found that intravenous injection of 6 cc. of a 5 per cent solution of sodium glycocholate into a rabbit weighing 1,010 gm. caused a diminution of the heart rate from 240 beats per minute to 120 in 10 hours. Twelve hours later the pulse had returned to normal and the animal appeared entirely well. The pulse frequently became very irregular. These experiments were repeated with taurocholic and cholic acids, with the same results.

¹ In 1863 (1604, p. 400): "Es bleibt mir nun noch übrig die Versuche aufzuzählen, welche ich mit den übrigen Gallenbestandtheilen angestellt habe und ich berichte hier zuerst über die mit den Gallenfarbstoffen unternommenen. Ich konnte mit den zwei wesentlichen, dem Cholepyrrhin und dem Bilifulvin (Hämatoidin) experimentiren, die beide in einer concentrirten Seifenlösung bis zur Sättigung derselben gelöst, und so Kaninchen verschiedener Grösse, meist indess kleinen, injicirt wurden. Die Lösung des Cholepyrrhin war tief dunkelbraun, viel dunkler als sonst Galle, die des Bilifulvins orange. Von beiden Lösungen wurden 6-8 CC. eingespritzt, es war jedoch niemals auch nur eine Spur von Einwirkung auf die Herzaction zu erkennen. Da die eingespritzte Seifenlösung durchaus keinen Effect auf die Herzbewegungen geäussert hatte."

The lymphatic heart and the blood heart were both laid bare by Röhrig, and 6 drops of a 5 per cent sodium glycocholate solution were put on the muscular tissue. The heart-beats diminished from 12 in the first 15 seconds to 4 at the end of 4 hours. Six hours later they returned to normal. He attributed the bradycardia to the action of bile acids on the lymph heart, the same as on the blood heart. Small doses may cause the lymph heart to cease beating while the blood heart continues to beat. Röhrig concluded that not only does bile cause bradycardia but that one constituent of bile, namely the salts, causes the slowing of the heart. Pigments, cholesterol, glycocoll, and taurin have no effect.

The same effects with subcutaneous injections of bile acids were not observed by Legg (1082, p. 209), who found that the systemic heart shows poisoning early and that the lymphatic heart begins to beat more slowly only after general poisoning has set in.

Dehydrocholic acid, 1 per cent solution, causes the heart to stop in 5-10 minutes; 2 per cent, in a few seconds; but desoxycholate, 1:1800 solution, brings the heart to a standstill in 1 minute. Therefore, to the isolated frog's heart, desoxycholate is twenty-five times more poisonous than dehydrocholate, according to Neubauer (1367).

According to Rowntree, Greene, and Aldrich, the bile salts in the blood are increased in experimental obstructive jaundice, and may contain from 2.5 to 6.0 mg. They used their modification of the Pettenkofer reaction. There was no relationship between high bile-acid content in the blood and bradycardia. They observed a slow heart more frequently in patients with intrahepatic involvement. Even with high Pettenkofer values, normal pulse rate or tachycardia was more frequently observed than bradycardia. Clinically, they found no relation between the quantity of bile salts in the blood and the heart rate.

The French school has maintained that the bile acids cause bradycardia. Widal, Abrami, and Brulé said that brady-

cardia is caused by bile salts, and concluded that jaundice without bradycardia indicates that there is bile pigment in the blood but no bile salts. Widal claimed that, since the fat metabolism is undisturbed, there is only partial obstruction and that the bile salts gain admission to the intestinal tract. Lyon-Caen (1152) and Parisot found the entire action due to bile salts. In normal man the intravenous injection of bile-salt solutions rarely causes bradycardia, according to Dumitresco-Mante and his associates (502).

Cholesterol.—Intravenous injections of cholesterol have been made repeatedly. The difficulty is in getting a suitable media, as cholesterol is insoluble in satisfactory intravenous solutions. Hence, most of the reported harmful effects of cholesterol on the heart were due to the menstruum, the mixture, or the emboli made by the cholesterol itself. There is no satisfactory evidence that cholesterol retards the heart rate. Hypocholesterolemia or hypercholesterolemia are not associated with variations in the heart pulse rate.

Other substances in the bile have not been shown to have any effect on the heart.

Calcium and potassium.—A disturbed calcium balance in obstructive jaundice and a marked diminution of calcium in the heart muscle were found by King, Bigelow, and Pearce; and slowing of the pulse was attributed to removal of the stimulating effect of calcium on the heart. (The effect of calcium and potassium on the heart will be discussed later.) The total calcium in the whole blood and blood serum is normal in jaundice, but much question has arisen concerning the available calcium.

LIVER

In obstructive jaundice, of course, there may be injury to the hepatic cells, also increased pressure in the intra-hepatic ducts. By way of the former, bile constituents may reach the blood stream. The increased pressure in the ducts may act as a mechanical factor, causing reflex diminution of the pulse rate.

Slow pulse has frequently been found in experimental animals with liver injuries, according to Finsterer. He explained the slow rate as due to the absorption of the bile acids, resulting in a strong cholemia. In rupture of the liver the bile may pass directly into the veins and circulation. He suggests that the slow pulse is a valuable aid in the diagnosis of liver injury. Diminution of the pulse in two cases of gunshot wounds of the liver in man was reported by Ricciuti.

A number of investigators have sought for the point of action of bile and its method of causing this peculiar heart action. Many have attributed the action of the bile to the bile acids and have tried to show particularly that the bile acids act on the nerves and ganglia.

NERVES

Bradycardia can be caused by stimulation of the central nervous system, and the impulse carried by way of the vagi, causing a slow rate, hence cardio-inhibitory; or by action on the accelerator nerves, preventing the stimuli from going through to the heart, and normally increasing the subnormal rate. Bile may also act on the intracardiac ganglia. Atropine paralyzes the nerve endings, preventing outside impulses from coming to the heart.

The first extensive experimental investigation of the action of bile on the heart was made by Röhrig. He injected bile intravenously and observed a slowing of the heart. The vagi were then cut and bile was injected, causing a slight slowing of the heart. He concluded that bile causes a specific damage to the excitomotor heart ganglion. Landois, 1863, was the first to section the vagi and sympathetics and inject bile into the blood stream, causing a diminution in the heart rate. He then concluded that bile acts directly on the heart. Feltz and Ritter (571) concurred.

Large quantities of bile were injected by Fasce into dogs and rabbits, which caused the pulse to increase many times. He ascribed this action to the bile constituents. In icterus and also in experimental animals the pulse was either in-

creased or normal; the tachycardia was due to traumatic irritation or to fever.

Atropine has no influence on the pulse when given after bile injection, as reported by Braun and Mayer. The action of bile is not on the intracardiac vagus endings but on the muscle. Weintraud (2068) found that atropine causes the pulse, which has been slowed by bile, to increase, and explained the slowing as due to central stimulation of the heart's "slowing apparatus" by bile.

It was reported by Betz that the tone of the heart is augmented by bile salts but that there is a diminution in diastole. Double vagotomy has no effect. De Bruin (435) found that bile salts do not affect the pneumogastric nerves.

Rabbits with the left vagus cut were used in experiments by Meltzer and Salant (1265). A minimal current was used to determine the inhibitory effect on the peripheral end of the vagus. Enough bile was then injected intravenously to cause a distinct fall in blood pressure. Stimulation of the peripheral end of the vagus showed that there was no loss in irritability but rather an increase. A second injection of bile was then made. Inhibitory effect of the vagus continued intact as long as there were any signs of pulsation of the heart. Atropine did not entirely prevent the effect of bile on the heart, as the heart could be brought to a standstill after complete atropinization.

In 1876 Legg found that bile acted on the heart ganglion system and that this action could be prevented by atropine. He thought, therefore, that the slow heart in jaundice was due to the action of bile on the ganglia. Ewald, Riegel, Grob, Laveran and Teissier, and Steiner endeavored to locate the point of action of bile on the heart. Some of these investigators stated that the ganglion was actually injured chemically, while others referred to the action as similar to that of atropine. Blay concluded that bile acts as a disabling agent on Remak's ganglion of the sinus.

Bile acts on cardio-inhibitory fibers, according to Röhrig,

1863; Feltz and Ritter, 1874; Spallitta, 1887; and Brandenburg, 1903. Spallitta concluded, from experimental observation, that bile (10 per cent salts) and atropine cause the heart to continue to beat longer than does bile alone, and that bile does not act on the central nervous system, because an excised frog's heart, placed in a glass tube in salt solution or salt and serum, and continuing to beat, can be influenced by bile after all the influence of the central nervous system has been cut off. Bile from the ox, dog, sheep and goat each have the same effect. Sodium glycocholate and sodium taurocholate act in like manner.

Bradycardia, according to Steiner, is not due to stimulation of the ends of the vagi by bile, for a slow heart rate appears even after paralysis with atropine. Bile placed on the posterior surface of the heart of the frog causes the heart to come to a standstill at once. Bile put on the anterior surface causes a decrease in pulse rate after a few minutes. If the ventricle is cut off after a Stannius' ligature has been placed, the pulsations of the sinus continue, but immediately stop when bile is applied to the sinus. If the ligature is applied to the heart, the sinus removed, and the ventricles cut off, the auricles continue to pulsate even after the application of bile, with no change in rate. Therefore, Steiner concluded that bile acts on the sinus ganglion and not on the auriculoventricular ganglion.

Rhythm is not disturbed, according to Lian (1592, cited) and Lyon-Caen (1151); but the actual period of contraction of the heart muscle is increased. Parisot, in experiments with ligature of the common duct in rabbits, found that the cardiac contraction diminishes but is otherwise not modified by atropine. The cardiac contractions are not altered by section of the cardiac nerves. Lian noticed, late in jaundice, a disassociation of the auricles and ventricles and found that atropine sulphate, 0.001 gm., causes a slight increase in the contraction of the muscle.

Electrocardiograms of jaundiced patients show a nervous

(not a myocardial) origin of bradycardia, according to Dumitresco-Mante and associates (502).² Hypotonia or hyperamphatonia is in close relation to blood changes. Hypercholinemia and hypercalcemia are always present in bradycardia; and hypocholinemia and hypocalcemia in the patients with tachycardia. The atropine test is positive in all cases with bradycardia. The presence of either bile salts or bile pigments, or both, is not constant. A solution of bile salt injected intravenously into normal men rarely causes bradycardia. Choline is the most important factor in bradycardia.

Age is a factor in the bradycardia of jaundice, according to Buchbinder (293), who experimented with young pups; but calcium variations in the blood during the different stages of the obstructive jaundice have not been recorded.

HEART MUSCLE

Other investigators, Ranke and Traube, thought that bile salts act on the heart muscle, actually causing alterations of the muscle substance. Löwit stated that bile salts act first on the ganglion and then on the heart muscle. Schack, and Bunting and Brown, observed myocardial degeneration. The latter found that bile causes a definite degeneration of the heart muscle, which can be observed by microscopic examination following intravenous and intraperitoneal injection of bile and bile salts. Feltz and Ritter (571), following the injection of bile into the crural vein of a dog, observed a bradycardia of 18 pulsations per minute. Because crystals were found in the blood following the injection, they thought that the bile acids act on the blood and the blood cells.

Intraperitoneal injection and direct application to the heart of a frog was made by Lyon-Caen (1152). Cardiac tracings showed the chronaxia of ventricles and auricles. Concentrated solutions augmented the chronaxia of the heart-

* "CONCLUSIONS GÉNÉRALES": "Dans les cas d'ictère étudiés par nous, la bradycardie ictérique, qui était une bradycardie totale, nerveuse, ne relevait pas toujours d'une simple hypertonie vagale. L'hypervagotonie pure classique des ictériques est rare; on trouve beaucoup plus souvent des ictères hypoamphotoniques, des ictères hyperamphotoniques, et même des ictères hypersympathicotomiques."

muscle fibers. At first the solutions seemed to act on the auriculoventricular fibers (fasciculi of Gaskell). The cardiac conductivity was diminished by a 1 per cent solution of bile. The excitability was not diminished unless solutions of greater concentration than 4 per cent were used.

It was found by Landois that small doses of whole bile or bile salts given intravenously or painted on the excised heart cause the rate to increase, but that large doses act so quickly that the increase of the pulse rate is not noticed and only the decrease observed. Landois, contrary to Traube, found no primary inhibitory action on the nerve and concluded that bile affects the muscular-motor-nervous system of the heart. But Traube replied that the basis for these conclusions lay in the quantities used and the method followed by Landois and by Röhrig. Traube and Leyden attributed the effect to the destruction of the blood corpuscles, which, in turn, caused malnourishment of the heart. Strong solutions of bile or bile salts, they concluded, act directly on the muscle of the heart.

Wieland and Hildenbrand, making their investigations on the excised frog's heart, observed that the action of cholic acid is similar to that of the digitalis group and that high concentration brings the heart to a standstill immediately. Cholic-acid poisoning of the heart cannot be washed out after a certain level has been reached; atropine has no effect on the poisoning; and cholic acid has a saponin-like action on the frog's heart. Ruling out the vagus action, he said that atropine has no effect on the poisoning of cholic acid and that there is no incubation period, especially when the acid is in high concentration. In low concentrations the action of cholic acid on the heart muscle and skeletal muscle is reversible and, in this way, is also similar to the action of the digitalis group. Cholic-acid poisoning of the heart causes slowing of the pulse, diminution in diastolic filling, systolic heart failure, diastolic heart failure in higher concentration, and rhythm alteration as to irregularity and grouping of pulse beats. All of this poisoning is similar to that of digitalis

poisoning. He³ concluded that there is a chemical action between cholic acid, or desoxycholic acid, and blood serum, on the one hand, and cholic acid and heart muscle, on the other, causing a chemical combination which results in cessation of the heartbeat. When the combination is broken and the cholic acid washed out, the heart begins to beat again. Thus, serum and desoxycholate form a reversible combination; the heart reacts quickly, according to the quantitative variations. Albumin most likely combines with desoxycholate; the other proteins, less likely. Desoxycholate in the serum is partly bound and partly free. The free portion acts on the heart and is reversible later; thus the serum partially inhibits the chemical action of the bile acid. Several substances—such as oleic acid, ether, xylol, animal charcoal, or camphor—cause this poisonous action to cease. This detoxification is noticeable if Ringer's solution and serum are used. The removal of the poisonous action of the desoxycholate is most conspicuous. The surface action seems to be a more plausible explanation than the chemical combination. These substances detoxify so thoroughly that the heart again returns to normal rate and rhythm after it has been stopped by bile acid. It would appear that the action of desoxycholate on the heart is similar

³ Wieland (211) found that the serum and desoxycholate have a reversible affinity for each other: Serum *minus* Desoxycholate \rightleftharpoons Serum *plus* Desoxycholate. For erythrocytes a concentration of 1:7,250 is not harmful; this same concentration does not affect the excised frog's heart. The mass action of the serum is reversible and is able to loosen the combination between the heart and the bile acid. Thus the poison can be washed out of the heart quickly with serum. If the heart is poisoned with bile salts in Ringer's solution, the equilibrium is: Heart *minus* Desoxycholate \rightleftharpoons Heart *plus* Desoxycholate. Now the combination on the left side is very strong, and only a small amount of desoxycholate remains free in the Ringer's solution. If serum is added, the free acid will be bound and a balance established between bile acid in the heart and serum, thus freeing the heart of the harmful amount which it has in combination. There may be a practical relationship of this nature as an explanation of cholemia, and many physiologic processes.

Wieland also observed that when bile acid is put in Ringer's solution the heart muscle very readily takes it up and combines with it, causing the heart to come to a standstill. Since the bile acids have an affinity also for serum, the combination of the heart and bile acid can be broken down by washing the heart with serum, thus bringing about a chemical equilibrium between the heart and bile acids and the serum and bile acids.

to the fatiguing of the heart muscle. The recovery is physiologically similar; even a heart poisoned with sodium desoxycholate cannot be caused to return to normal by washing with Ringer's solution, but can be speedily returned to normal after washing with serum or serum in Ringer's solution.

Bile acids act similarly to digitalis on the heart (Manta). Perfusion of the frog's heart with dilute bile causes the heart to come to a diastolic standstill (Mijerson). But Ashur presents a new view: he states that, since bile and extract of liver cause a slowing of the heart, the physiologic concentration of cholate from the liver passes into the blood to serve as a physiologic regulator of the heart.

The conclusion was reached by Marey and Kleinpetter that the slowing of the pulse is due to the fall in blood pressure caused by bile in the blood, and not by its action on the heart muscle.

Weintraud (2068) declared in 1894 that an explanation of bradycardia in icterus had not been made clinically or experimentally.

Blood obtained from a dog with jaundice causes a bradycardia when given to another dog, according to Roger (1592).

There are many causes of diminution of the heart rate; and when many disturbing factors can be and are modified at the same time, interpretation is difficult. For example, a patient with jaundice is usually inactive physically. He spends much time at sleep or at rest in bed. The inactivity with decreased metabolism probably accounts, to some extent, for the bradycardia. The definite influence of bile on the heart in icterus is yet to be proved.

ACTION OF BILE ON THE BLOOD PRESSURE

Jaundice is frequently accompanied by a weak pulse. Clinical observations were made by many physicians a century ago. Later Landois, Röhrig, Feltz and Ritter, Löwit, Frerichs, Rywosch, Traube, Legg, and many others found a

diminution in blood pressure in experimental animals, following the intravenous injection of bile or bile salts.

The first kymographic tracings of the effect of bile or bile salts on the blood pressure were made by Traube in 1864. He used *natrium choleinicum*. The next tracings were made by Löwit, 1882, who, using sodium cholate, observed that large amounts caused a depressed blood pressure and that small amounts increased it. Intracarotid injections of bile salts caused a rise in blood pressure. Blood-pressure readings were taken from the carotid artery by Meltzer and Salant (1265) in their experiments on rabbits under ether. Rapid injections of 0.2–0.3 gm. of bile salts into the jugular vein caused a fall in pressure of 60–70 mm. of mercury; and with a slow injection of 1.0 gm., the fall was only 12–15 mm. Concentrated solutions had marked effect; dilute solutions, slight effect. Ten cubic centimeters of ox bile given slowly intravenously had very little effect, but 2 cc. introduced rapidly had a very marked effect, on the blood pressure, and in many instances caused death. Whole beef bile, undiluted, diluted, and also inspissated, was used. Meltzer and Salant considered the hemolytic theory disproved.

Thrombosis, emboli, hemolysis, and a marked fall in blood pressure were observed by Horrall following intravenous injections of various kinds of bile and many varieties of bile salts, especially when given rapidly. Numerous tracings were made. Intraperitoneal injections caused a similar, but slower and more gradual, fall in blood pressure. There were no sudden dips, as found following intravenous injections.

Bile given intravenously has no effect on the blood pressure, according to Edmunds. Intravenous injection of 5 cc. of 1 per cent solution of sodium glycocholate has almost no effect on rabbits under anesthesia, and the same quantity of sodium taurocholate causes only a slight change.

Small amounts of bile acids given intravenously to anesthetized animals increase the blood pressure, and large

amounts decrease it, according to Still. Marey (1200) observed increased blood pressure in jaundice. Most of the observers found the blood pressure decreased in clinical cases.

Sodium dehydrocholate⁴ was injected intravenously into 14 men by Adlersberg and Taubenhau. In about two-thirds of these patients there was a fall in blood pressure of from 12 to 30 mm. of mercury. Numerous intravenous injections of the same solutions, using the same quantity, into dogs were made by Regan and Horrall without causing a fall in blood pressure or change of heart rate. Large quantities, two or three times this amount, were given to small dogs, causing a marked sudden fall in blood pressure with a slowing of the heart. When 10 cc. of sodium dehydrocholate were injected, very cold or very rapidly, death followed a fall of blood pressure. At times there were rises in blood pressure at the beginning of the injection, but only for a few seconds and only a few millimeters.

The fall in blood pressure is attributed by Strecker (1852) primarily to the action of bile on the heart muscle, but the slowing of the pulse is ascribed to the action of bile on the vagus.

RÉSUMÉ

Bradycardia is not constant in any type of icterus.

Atropine does not affect the bradycardia in some cases. Experiments show that hypervagotonia is not to be accepted as being the cause of the bradycardia.

If the bradycardia were caused by bile acting on the vagus and thus slowing the heart, atropine would increase the heart rate.

Bile salts in the bile of a dog affects the conductivity in the heart of a frog with slow rhythm and dissociation of the auriculoventricular rhythm, and stops the contraction of the ventricles without modification of the chronaxia (Lyon-

⁴ The intravenous dose of sodium dehydrocholate, 20 per cent solution, for a man weighing 150 pounds is 10 cc. The foregoing dose used for a 20-pound dog was, accordingly, many times greater when weight was considered.

Caen). The intravenous injection in man of 2-3 gm. of bile salts in a solution four to five times more concentrated than is observed in jaundice does not always cause bradycardia (Chabrol and Maximin).

The idea of bile salts being the cause of bradycardia was rejected by Dumitresco-Mante, who thinks the cause lies in the variations of calcium and choline in the blood.

The retention of bile itself modifies the liver and gall passages. It has been shown experimentally that increased pressure within the gallbladder causes slowing of the heart rate. It is interesting to note that bradycardia most frequently occurs in cancer with obstruction of the outflow of bile.

Digestive disturbances with the failure of fat metabolism and with an increase from the normal 5 per cent excretion of fat in the feces to more than 40 per cent when bile is absent from the intestine (337, p. 114) suggests a possibility of absorption of a toxic substance. It must not be forgotten that, when bile ducts are obstructed by a new growth, the pancreatic ducts are frequently obstructed at the same time.

Emaciation and malnutrition are present in late jaundice.

Functional disturbance of the liver with variations in nitrogen metabolism must be considered.

CHAPTER XIV

ACTION OF BILE ON SKELETAL MUSCLE

THE first observation of an alteration of muscle with a visible structural change caused by bile was made by Budge in 1852. Bile of frog was placed upon the exposed muscles of the frog's leg, causing a rapid contraction. Incised muscles, when touched on the cut surface with bile, contracted more vigorously than the uncut. Kühne applied gallbladder bile to the thigh muscle of a frog, causing a very strong contraction, which lasted longer than a physiologic action. The nerve of fresh muscle-nerve preparation was touched with diluted bile, causing a spasm of the muscle. Bile applied to the cross-section of a muscle caused contraction. Ether-alcohol extract of bile, diluted to 2-3 per cent, caused contraction. Bile salts in solutions stronger than 6 per cent caused one sudden contraction and then no more. Bile salts and bile, as observed by Ranke in 1864,¹ caused the muscle to become lame and the cells to be altered chemically. Sodium glycocholate, 0.5 per cent, was injected into the rear legs of frogs, causing the muscles to become very hard, so that they would not react to electrical stimulation. On washing with salt solution, the muscle did not recover. The failure to restore the action of the muscle caused Ranke to conclude that a chemical change had taken place in the muscle. The muscular-motor theory was advanced by Traube in 1864. Schack, 1868, without knowing of the work of Ranke, showed that bile causes a loss of the irritability of the muscle, its histologic appearance changing so that the cross-striations are lost and the contents of the muscle cell coagulated.

Muscle failure in jaundice and following injection of bile

¹ "... gallensäuren Salze eine lähmende Wirkung auf die Muskeln. . . . Diese Lähmung ist nach seiner Meinung Folge einer chemischen Veränderung der Musculatur."

was observed by Feltz and Ritter (571) in 1871, suggesting that muscle failure is due to altering (*altérée*) of the blood. No microscopic evidence has been found of changes in the red blood cells in icterus, but inconstant changes in the viscosity of the blood have been observed. Bile salts affect the contractility of the muscle substance.

Striated muscle cells were dissolved in the presence of bile by Bouchard. This resulted in anatomic lesions, and the slowly developing intoxications arose from the setting-free of toxic substances which were formed by the decomposition of the cellular elements. In part from these observations he formulated his widely heralded autointoxication theory in reference to jaundice.

Irregular contractions of the muscles of the rear limbs of frogs were observed by Legg (1080),² following intra-aortic

² In 1880 (1082, pp. 199-201): "There were the irregular contractions of the muscles of the limbs as the injection passed into them, rigidity and hardness immediately after the injection, and an absence of contraction on the application of electricity to the sciatic nerves. Knowing, however, that bile acids will coagulate albumen, as a 1 per cent solution will cause turbidity in white of egg, it would seem that the appearances described by Ranke would be very fully explained by the chemical action of the bile acids upon the albuminous bodies of the muscle.

"I was thus led to make a series of experiments in which the bile acids should not be immediately injected into the muscle, but should act by the natural process of absorption. The solution of the bile acids was injected into the lymphatic sac or under the skin of frogs. The amount given varied from .05 to .3 grams. Twelve experiments were made; and in nearly all no change in the curve traced by the myograph could be detected after the injection of the bile acids, the observations beginning immediately after the injection of the bile acids, and lasting up to the time that the muscles would respond to any amount of electricity that I was able to bring to bear upon them.

"The method used was as follows: the sciatic nerve was prepared, carefully avoiding all injury of blood vessels; the tendon of the gastrocnemius was attached to a string, and separated from the heel. The frog was then put into a moist chamber and the string attached to the tendo-Achillis, fastened to a telegraph lever writing on a revolving cylinder. The sciatic nerve was then irritated by means of electricity from a DuBois-Reymond's coil; it was applied no oftener than once every minute, and only of such amount as to cause the muscle to contract. In the first two or three experiments the injection was given before the muscle was ready.

"As samples of the other, I detail two of these experiments. Jan. 22nd. Excellent normal curves obtained. 0.1 gm. of bile acids injected under skin of back. No change in the curves save that they grow smaller in height from 15 to 60 minutes after injection.

"Feb. 2nd. 0.3 gram of bile acids injected under skin of back, no change in the normal curves from 19 to 92 minutes after injection."

injection of 10 cc. of 1 per cent bile acids. This was followed by rigidity and hardness; their stimulation of the sciatic nerve caused no effect, and he concluded that bile acts as a chemical on the albuminous part of the muscle. Bile acid, 0.5 gm., was then injected into the lymphatic sac, causing no effect on the muscle.

A 1 per cent solution of sodium taurocholate was applied to the gastrocnemius and sartorius muscles of a frog by Rywosch (1659) in 1891. The muscles contracted strongly and shriveled, then stiffened as the myosin coagulated, and after a few minutes were so rigid that no amount of electrical stimulation would cause motion. The cross-striations were not visible under the microscope, and the myosin was entirely congealed. A more dilute solution, 0.5 per cent bile salts, caused the muscle to contract for a longer time, and coagulation was delayed for 2 hours. This action, according to Rywosch, cannot be compared with that of the bile in the blood stream, as the strength of the bile salts was much greater in the experiments than would ever occur in jaundiced blood. Sodium glycocholate and sodium taurocholate—0.5 per cent, 0.8 per cent, and 1.0 per cent solutions—were used, and from time to time the muscle was stimulated with a Du Bois induction apparatus. He concluded that sodium taurocholate acts more vigorously than sodium glycocholate on muscle; that chenocholate is the most poisonous; that choloidinic acid and hyocholic acid are only slightly more active than glycocholic; and that the bile salts act on the muscle as a saponin substance.³

Paralysis of muscle is produced by bile, as shown by Meltzer and Salant in 1906. Many investigators have thought that bile acts directly on the muscle, not only in injection experiments but also in icterus. Large quantities of

³ Rywosch (1658, p. 119): "Im Grossen und Ganzen zeigen die gallensäuren Salze auch in der Einwirkung auf die Musculatur eine auffallende Aehnlichkeit mit den Saponinsubstanzen. Dieselbe zeigte sich nicht etwa nur am ausgeschnittenen Muskel, sondern auch bei Versuchen an ganzen warm- und kaltblütigen Thieren."

rabbit gallbladder bile were injected into the lymph sacs of frogs, causing paralysis of the rear legs long before there was any sign of paralysis elsewhere. This paralysis was caused by the bile coming in direct contact with the muscles.

The writer has frequently dropped a small amount of bile or bile salts on exposed muscle, striated or nonstriated, and observed twitching and fibrillation, followed by paralysis when the quantity was increased. If washed off quickly with physiologic salt solution or serum, the more severe signs did not occur and the muscle returned to its normal condition.

Increased chronaxia of the muscle, following the application of bile salts, without modification of the chronaxia of the nerve, was observed by Lyon-Caen in 1925. The action was more prompt and more intense on slowly acting muscle than on the rapidly acting muscle.

Feltz and Ritter, Traube, Schack, Ranke, Ewald, Riegel, and Grob thought that in icterus bile acts on the muscle; Legg and Brandenburg concluded that the bile acts not only on the muscle but also on the nervous apparatus.

Working with the gastrocnemius muscle of a frog in Ringer's solution, Wieland, in 1920, found that spontaneous fibrillations occur with cholic acid but never with desoxycholic. The quantitative toxic relation is cholic acid, 1:800, and desoxycholic acid, 1:6400. The actions of both acids on isolated skeletal muscle are similar to their actions on the heart muscle.

In an experiment by Tsurata (1949) antagonizers caused bile salts to act less vigorously on muscle-nerve preparation of the frog. The anti-substances which were added to the bile-salt solutions prevented tetanus of the muscle. Lecithin and phosphatides were the most active. Since the action of bile on the muscle differed from that on the nerve, it is suggested that there is a natural and more efficient protective substance in the nerve (Tsurata).

RÉSUMÉ

It is difficult to evaluate these observations, particularly since the quantity of bile salts in the blood stream in icterus is very small in comparison with that used in the foregoing experiments. In jaundice we are not dealing with the action of bile or bile salts alone.

CHAPTER XV

EXCRETION OF BILE IN THE URINE AND ITS TOXIC ACTION

THE fate of bile in the body has been dealt with elsewhere in this volume. This chapter has to do with the role of the kidneys in the elimination of the main constituents of bile, with the effects of these substances on the kidneys themselves, and with the toxicity of urine containing such substances as are derived from bile and eliminated by the kidneys during jaundice.

It has been known for a long time that bile pigments appear in the urine in jaundice and, more particularly, in obstructive jaundice. The urine becomes deeply colored early in jaundice. The first record of such an observation was written by Hippocrates. A jaundiced patient can very easily detect the increased color of the foam on urine that has just been passed, or after shaking a specimen.

BILE IN THE URINE

In early jaundice there is an increase in the total quantity of protein in the urine. It is rarely absent. As the jaundiced condition is prolonged, the albumin in the urine gradually increases in quantity, changing from the debris type to cellular, then to granular, and finally to large quantities of hyaline casts.

Following ligation of the common duct in the first experimental animals, the urine was discolored. The experimental work of Tiedemann and Gmelin, 1827, was designed to discover the way in which bile reaches the blood and thence the urine in obstructive jaundice. It was found by the foregoing workers and Harley (767) that the portal of entrance into the blood is primarily through the thoracic duct. This work was

based on the assumption that all constituents of bile are formed in the liver.

Sugar is rarely met with in the urine in jaundice. There is a reciprocal relation between the formation and discharge of bile from the liver and the formation and discharge of glycogen (Saadi-Nazim and Usuelli).

The terminology *bile in the urine* usually refers to Gmelin's reaction; and this depends on the presence of pigment, which reacts with nitric acid, giving various colors according to the type of bile pigment present, so that most of the older works, and our textbooks today, refer to bile in the urine according to the Gmelin test, or some modification of it, which means bile pigment in the urine.

The recent work of Mann gives evidence that at least some of the constituents of bile are formed outside the liver, and suggests that when the portal of exit of bile through the liver is raised, causing retention in the blood stream to a sufficiently high concentration, the kidneys begin to remove the bile constituents and excretion takes place in the urine.

Other experiments were carried out by the introduction of whole bile orally, intravenously, intraperitoneally, and subcutaneously; and the excretion of pigment in the urine was observed. However, it was not until attempts were made to deal with the constituents of bile separately that any real understanding was reached as to the role played by the kidneys in the elimination of bile.

Bile pigments appear in the urine in various forms, as seen by the color of freshly passed urine. The jaundiced urine may be colored a deep yellow, orange, reddish brown, dark brown, greenish black, or almost black.¹ The orange and reddish colors are due to bilirubin; the green, to biliverdin; and the black, to bilihumin. These coloring matters show characteristic absorption spectra. Usually the examination shows bilirubin and its various oxidation products. If the urine stands for a time, rapid changes take place in the bilirubin,

¹ The urine is almost black in black-water fever.

as it is very sensitive to changes in alkalinity, light, and oxygen. When bile pigment is present in the urine in complete obstructive jaundice, the color is usually due to bilirubin, as urobilin, the pigment in normal urine, is absent because of the failure to produce it in the bilirubin-free intestinal contents.

The injection of whole bile and bile salts intravenously into dogs by Feltz and Ritter (565, 566) caused bile pigment to appear in the urine, the amount of coloring material being in proportion to the amount of bile injected.

Following ligation of the common duct in the dog, Snell, Greene, and Rowntree (1798) did not find pigment in the urine until the second day. Frerichs always found bile in the urine within 48 hours after ligation.

When bilirubin is injected intravenously into rabbit, dog, or man, a small amount may appear in the urine. All bile pigment is not eliminated by way of the urine, even in complete obstructive jaundice. Frequently in incomplete jaundice, or very early in jaundice, crystals of bilirubin can be found, by means of the microscope, in cells or in casts in the urine. These observations are frequently positive before the ordinary chemical tests can demonstrate bile pigment or salts in the urine.

Hoppe-Seyler (842), Kühne (1034), Leyden (1105), and Huppert (873) found small amounts of bile salts in the urine when these salts were present in the blood in excessive concentrations.

Bile acids were found by Kühne (1034) in the feces of dogs on a potato and fat diet, with no evidence of any absorption from the intestine. A modified Pettenkofer reaction with sugar and sulphuric acid solutions was used for testing. The urine contained no paired bile acids, but only unpaired nitrogen-free cholic acid, after intravenous injection of bile in the dog. Twenty hours after ligation of the common duct in a dog, the urine gave a marked reaction for bile acids and pigment. Frerichs (634) failed to find bile acids in the urine in cases of

jaundice, using his modification of the Pettenkofer reaction. He then injected large amounts of pigment-free bile into the blood of animals and found what he believed to be bile pigment in the urine, but no bile acids. This pigment corresponded to the products formed outside the body by the action of sulphuric acid on bile acids, which led to the conclusion that the same reaction takes place in the body. He also found that when pigment appeared in the urine it was accompanied by albumin, and that there was often hematuria. Examination of the urine for bile acids in 19 cases of jaundice, using the Pettenkofer test with sugar and sulphuric acid, failed to reveal any of the biliary acids, so Frerichs concluded that in his experiments the biliary acids were not excreted in an unchanged condition in the urine.

Large quantities of pigment-free bile were then injected into the blood of living animals, and a pigment was excreted in the urine. This coloring matter had the characteristic properties of bile pigment and corresponded in its behavior with the products formed by the artificial action of sulphuric acid on bile acids. Unchanged biliary acids were not found along with the coloring matter, but leucine was usually present. He therefore concluded that he had proved that bile acids are transformed into bile pigments. When large quantities of bile acids are injected into the blood, they completely disappear within a short time, not because they are voided but because they have undergone changes or have passed into the tissues.

A quantitative examination of bile acids in the urine and blood was made by Neukomm (1376) in 1860, using the Pettenkofer reaction with sugar solution and color standards; but it was found that the estimations were interfered with by other substances in the urine. Sodium glycocholate was injected very slowly intravenously into dogs in amounts of 0.8–2.2 gm. in 10 cc. of water, and only an occasional slight trace of bile acids was found in the urine. In cases of cirrhosis of the liver with jaundice, as well as in cases of obstructive jaundice, only slight traces of bile acids appeared in urine.

The test for bile acids in the urine did not appear until much later. The Pettenkofer test, with its various modifications, is not specific for bile acids, either in the urine or in the blood. The determination of sulphur in the urine of dogs, which normally secrete mainly sulphur-containing bile acids, is not reliable. Neither is the obtaining of crystals characteristic of the various bile acids feasible, because of the difficulty of technic and because this test is not quantitative. As yet, only an approximate test for bile salts in the urine has been developed.

The phenomena of three types of jaundice appear in the urine just as they appear in the blood. The bile pigments alone may appear in the urine, or the bile salts alone, or the bile salts and bile pigments together. Variations of other constituents of the urine—such as urea, uric acid, sulphates, chlorides, phosphates, leucine, and tyrosine—may increase or decrease according to the type or degree of conditions and the other variations of body metabolism associated with jaundice, but are not directly related to the toxicity of the bile acids.

Following the intravenous injection of 1.5 gm. of sodium glycocholate into a dog, Huppert (873) recovered from all the blood and urine only 0.14 gm. About one-fourth disappeared in the liver. The main part (two-thirds) of the injected bile acids transuded into the tissues; about one-twentieth was excreted in the urine; and a large part of that excreted by way of the liver into the gut was reabsorbed; the rest was eliminated in the feces. Leyden (1105) injected intravenously into a dog 1.5 gm. sodium glycocholate and recovered only 0.227 gm. in the urine in 24 hours. Following an intravenous injection of ox gall and bile acids, a small amount appeared in the feces.

Bile salts in jaundice are very insignificant: highest, 0.1–0.15 gm. per liter output in the urine, as contrasted with 10–12 gm. synthesized daily by the body. There is no parallelism between bilirubinuria and *cholaluria*, according to

Chabrol and Bénard (341). In the normal human urine there are no bile acids (Isaac). Whipple and Smith (2096) more recently reviewed the subject of bile acids in the urine and found that only in jaundice are there small amounts of bile salts, 200–300 mg. per day. There has been an extensive amount of work done on the phenomenon of the three types of jaundice, under the subject of “Dissociated Jaundice,” by Hoover and Blankenhorn in this country and by Lemierre, Brulé, and Garban and others in France.

In sudden complete obstructive jaundice both pigments and bile salts appear in the urine 24 hours before the conjunctivae are icteric. In dissociated jaundice either bile salts or bile pigments may disappear from the urine, after having appeared; or either may appear alone. In some cases of jaundice there appears to be a relationship between bile pigment and bile acids in the blood plasma and in the urine, while in other types of cases this relationship does not exist. In internal hemorrhagic extravasations and in toxic hemolysis without disease of the liver, bile pigment may be increased in the blood stream and excreted in the urine; but the bile salts may be absent, according to the most delicate test.

Urobilin is usually absent when much bile pigment is present in the urine. Bile pigment may be absent from the urine even though the tissues are deeply jaundiced. Casts, urinary sediment, or cells may be bile-stained, even though the urine gives no bile reaction to the simple tests. The bilirubin crystals may even be seen within the cells or casts without giving any chemical reaction indicating their presence. Bile pigments occur frequently in the urine, usually associated with obstructive conditions in the biliary passages or diseases of the liver without obstruction, and also in some diseases of the kidneys.

RÉSUMÉ

The appearance of bile salts or pigments in the urine may depend on the difference in production, diffusibility, or selective decreased efficiency of their normal portals of excretion.

Either the bile salts or pigment may be present in very high concentration in the blood plasma and yet not filter into the urine. The factors concerning the excretion of bile salts and bile pigments into the urine may be renal or hepatic. There does not seem to be any absolutely constant relationship quantitatively between bile pigment and bile-acid excretion. Each bile constituent must be tested for quantitatively before any conclusion can be drawn as to its presence in the urine. A positive Gmelin test means that bile pigment is present, and has nothing to do with bile acids or other bile constituents. Under normal conditions bile pigment and bile salts are found in the urine only in minute traces, if at all. In any condition in which the concentration of bile or its constituents in the blood is increased sufficiently, bile pigments may appear in the urine in large amounts. Elimination through the kidneys, however, never appears to become important for disposing of bile salts, since in severe jaundice only small amounts of these substances appear in the urine. The body has other effective ways of dealing with them.

EFFECT OF BILE ON THE KIDNEYS

The appearance of albuminuria, and at times casts and blood in the urine, in jaundice has been observed frequently, and various explanations have been advanced.

When bile was fed to white rats, Cooper found blood in the urine. Previously, similar observations had been made by Hoppe-Seyler, Huppert, and Bunting and Brown. De Bruin injected a rabbit intravenously with bilirubin in an alkaline solution, and casts and hemoglobin appeared in the urine. He concluded that bilirubin causes a parenchymatous nephritis. It is probable, however, that the effects observed by him were due to the alkali, since subsequent experiments have not confirmed this action by bilirubin, but with alkali alone.

Marked congestion of the kidneys, epithelial necrosis, minute hemorrhages, casts, and hemoglobin within the tubu-

lar lumen were observed by Bunting and Brown after intraperitoneal injection of bile into the rabbit. An extensive study was made by Werner of the changes in the renal cells of rabbits following subcutaneous injections of small quantities of ox and human bile. The cells of the tubules degenerated and were so altered that they became detached and filled up the tubules. This was attributed to a cytotoxic action on the kidney cells, producing a biliary or toxic nephritis. Following the injection either of 5 cc. of bile or of 0.5 gm. of bile salt, Werner found that, if the rabbit lived 24 hours, the Gmelin reaction was positive. There was a much more intensive altering of the kidney with purified bile salts than with the same quantity of bile salts in bile. Kidney epithelium first became yellowish and then stained with osmic acid; cells became detached and filled the lumen of the tubules; and pale hyaline casts appeared in the urine.

If there was sufficient damage to the liver, the urine usually contained albumin, casts, and even red cells. The blood nitrogen increased, and there was a progressive oliguria. In experimental work, with traumatism of the liver of dogs and rabbits, the kidneys were affected, even though the damage to the liver was not sufficient to cause a noticeable jaundice. Human pathology was reproduced in experimental animals.

The damaged liver tissue elaborates a toxin which acts on the kidney, according to Helwig and Schutz. Helwig and Orr reported the case of a boy with seriously damaged liver which was followed by extreme jaundice, albumin, casts and blood in the urine, oliguria, and increased nitrogen and creatinine in the blood. They concluded that the poisons from the liver acted on the kidney, causing a high-grade nephrosis. Cums-ton (411), in reviewing the work of French investigators, pointed out that icterus may accompany acute nephritis with very mild involvement of the liver.

A large percentage of all patients with jaundice have an associated kidney condition, as shown by albumin, casts, and increased blood urea. The increased blood urea usually ap-

pears somewhat later in the course of the disease. With increased kidney impairment the blood urea rises. There is also an increase of bile acids in the blood stream. The term *cholemic nephritis* has been applied to this condition of renal insufficiency. Usually prolonged retention of bile in the system causes degenerative changes in the renal parenchymal cells, as in the cells of other organs.

The following changes in the kidneys in 7 dogs were observed by Romeo, following ligation of the common duct: (1) degeneration of the epithelium, (2) glomerular distension and atrophy of the epithelium, and (3) toxic sclerosis. The functional alterations were: (1) nephrosis, single, followed by (2) oliguric nephrosis due to trophic glomerular alterations, which gradually reduce the filtering portion. The change from nephrosis to oliguric nephrosis took place about the thirty-fifth day of icterus. This work confirmed the observation of Feltz and Ritter (566).

It has been demonstrated more recently, by Horrall and Carlson, that all the toxic effects of bile upon the kidneys can be produced by solutions of pure bile salts but not by bile pigments; from which it may be concluded that the toxic effects upon the kidneys, owing to bile per se and not to pathologic conditions associated with jaundiced urine, are due to the bile salts, more specifically to the cholate portion.

THE TOXICITY OF JAUNDICED URINE

From the fact that bile is toxic, it might reasonably be inferred that jaundiced urine would also be toxic. This matter has received attention, especially by the Italian school. Colasanti and his collaborators have done extensive work on the toxicity of urine, and more particularly on the toxicity of urine in jaundice. They studied the relative toxicity of bile and urine and found that, when the liver functions normally, the toxicity of bile is at its maximum and the toxicity of urine at its minimum. Any condition interfering with the detoxifying action of the liver upon the blood increases the

relative toxicity of the urine. The toxicity of both bile and urine can be markedly reduced by filtering through animal charcoal.

Bile acids cause an increased secretion of urine, which is particularly noticeable in cases of ascites and edema (Stanojević, Bix, Kaufteil, Adlersberg, Wiegand); but there is no evidence as to the mechanism. Under ordinary conditions, however, bile acids cause an increased bile volume output which is associated with a decreased urine output; therefore there is a compensatory water mechanism between the liver and the kidney (Sekitoo, Yano). End products of metabolism are likewise cared for under pathologic conditions (Faludi). On the other hand, Lucke, working with residual oxygen and nitrogen in bile, concluded that a compensatory mechanism of the kidney and liver is not possible. In rabbits with phosphorus and carbon tetrachloride poisoning, causing deficiency in the liver, the blood chlorides increase conspicuously; therefore, there is a compensatory chloride mechanism (Maruno).

The pH of urine in obstructive jaundice and following the injection of bile acids is increased (Chashi, Kawada). The increase in pH is parallel with the increase in specific gravity and with the amount of bile acid injected (Kuramoto). The NH_3 output in dog's urine is decreased (Kawada), and Ca output in rabbit's urine is increased (Iwado). After ligation of the common duct, bilirubin is excreted by the epithelial cells of the urinary canals of the kidney, which (Saiki) is called a reciprocal mechanism; this is much more easily demonstrated in the dog than in the rabbit, as the renal threshold of the former is much lower. The renal threshold depends also on the type of bilirubin, for very little indirect-type bilirubin is excreted in the urine (Bensley). Since cholemia and uremia are clinically counterparts and influence each other, Matsuda thinks a hepatorenal disease should be recognized. This idea is further supported by the findings of Boyce and McFetridge in their 34 cases of liver deaths. They concluded that the water-soluble toxic substances released from

necrosed liver cells cause changes in the kidney cells. The kidney changes are secondary to liver obstruction.

The waste products of cellular disintegration are the chief cause of the toxicity of the urine in jaundice, according to Bouchard. The toxicity of jaundiced urine is greatly diminished when decolorized with animal charcoal. It has been shown more recently by Horrall that filtering either bile or urine through animal charcoal until decolorized actually diminishes the specific gravity, which is parallel with the diminution in its toxicity.

There have been numerous attempts to discover the exact substance in jaundiced urine that causes the increased toxicity: Neukomm (1376), Frerichs (634), Kühne (1034), Bellati (137), Colasanti (377), Huppert (873), and Feltz and Ritter (570). Brücke transplanted a ureter into the inferior vena cava in the rabbit, cat, and dog, shunting the urine into the blood stream, and concluded that death resulted from "nephrogene Gifte" and that there was a disturbance in the protein change, causing the formation of secondary active poisons. He also concluded that the kidney is not a filter organ. On the contrary, Marx and Heupke concluded that there are changes in the salts, organic constituents, and colloids in the blood; but no attempt has been made to determine the chemistry of the toxic substance. When the residual nitrogen was increased, tubular nephritis appeared; but the poisonous effects could not be produced by ammonia, alcohol-insoluble organic salts, urea, or urine pigments. The substance is thermostable, alcohol-soluble, and ether-insoluble, according to Okuizumi. When bile acids were fed, the urine was not the channel of elimination; and even in jaundice, very little of the bile acids was found in the urine by the Pettenkofer test. The taurocholic acid is probably broken up and eliminated as sulphates in the urine, according to Schmidt and Clark; but the cholic portion is eliminated as such in only a very small degree.

From experimental evidence there seems to be no adequate

explanation for the increased toxicity of jaundiced urine, at least on the basis of biliary constituents. Jaundiced urine, of course, may contain bile acids in combination with, or in the presence of, other substances, interfering with the Pettenkofer reaction. It has been shown by Lyon-Caen that the Hay test for decreased surface tension due to bile salts in the urine is very inaccurate in the presence of albumin in the urine, which unfortunately usually occurs in jaundice. Lyon-Caen found a lowered urine surface tension to be evidence that bile salts are present though bile pigment is absent. Bile salts, being diffusible, are more rapidly excreted through the renal filter; and, following complete icterus, bile pigment alone may be retained in the plasma, a condition known as *renal dissociation jaundice*.

The superficial tension of urine has been tested by the stalagmometer, which showed a tension of normal urine running approximately 950; with injection of salts of 3 gm. in 10 cc. of physiologic serum intravenously into a man, there was a drop in the superficial tension of the urine within 4 hours to 700. Urine returned almost to normal within 8–12 hours. With the injection of the same amount of bile salts into a person with hepatic disease, the superficial tension of the urine was depressed with the same rapidity as with urine from a normal person, and to the same extent; but recovery to the normal superficial tension took place over a period of 4–5 days. Bile salts provoke an increased toxic hepatitis similar to that caused by salvarsan and chloroform, thereby causing a retention of bile salts in the blood stream (Chabrol and Maximin [337]). In *ictère total* the superficial tension of the urine is between 700 and 850 (Bénard).

Bile acids were used by Lebermann to produce a diuretic action in patients suffering from oliguria and edema caused by decompensated heart lesions. Sodium dehydrocholate, 2.0 gm., given intravenously and by mouth to such patients, showed good results.

RÉSUMÉ

From the material presented above, certain general conclusions may be drawn. The kidneys normally play no role in the metabolism or elimination of bile pigments or bile salts, but their action in detoxification of the blood is complementary to that of the liver excreting mechanism. In jaundice the kidneys perform an emergency function in the elimination of bile pigments and to a lesser extent of bile salts, also to an unknown extent in the elimination of other toxic substances which would ordinarily be eliminated in the bile. In the process, damage occurs to the kidneys, which, though hardly to be termed nephritis, is associated with injury to the tubular elements, with characteristic symptoms of albuminuria, hematuria, and the appearance of casts in the urine. The toxicity of jaundiced urine is materially increased, owing to bile salts and altered organic substances as yet undetermined.

.

CHAPTER XVI

ACTION OF BILE ON THE UTERUS

BILE causes the isolated uterus to contract. Kehrer (992), in 1908, was the first to test the effect of bile and bile salts on uterine muscle strips in Ringer's solution. Fresh bile from gallbladders of dog and ox in concentrations of 0.10–0.20 gm. in 200 cc. of Ringer's solution caused increased contractions of the suspended strip; 1 cc. of bile caused the tone and activity to increase even to tetanus.

Experimenting with the excised uterus, Cantoni, in 1914, observed a decrease in contractions produced by bile and bile salts. This applied to the contraction of the pregnant uterus but never to the virgin uterus. The amplitude was never increased, but the tone was increased even to tetanus. High concentrations depressed the action of the uterus. These results with the muscle of the uterus were similar to those of Berti (160), in 1909, with intestinal strips.

The automatic contractions of the uteri of virgin and pregnant guinea-pigs were studied by Hofbauer, 1928. The whole uterine horn, together with a strip of pregnant uterus 4 cm. long, was immersed in 50 cc. of Locke's solution. The spontaneous contractions were inhibited by the addition of 1 cc. of $\frac{1}{4}$ of 1% sodium glycocholate. Pituitrin caused increased contractions. The effect of bile on the virgin, early-pregnant, and late-pregnant uterus was the same. A hyperbilirubinemia has been reported in pregnant women by Schlüns and by Sustrunk. It occurs in about 67 per cent of the cases, according to Lepehne and others. This has been referred to under the subject of bilirubin.

The cause of abortion and premature labor has been attributed frequently to the action of bile or bile acids on the uterus, but probably here the cause was general intoxication.

In very severe jaundice, the bile in the blood does not have sufficient concentration to affect uterine contractions *in vitro*. Nontoxic bile-pigment retention does not explain eclampsia. If there were a sufficient increase in the toxic bile salts, these assumptions could have a possible basis. Jaundice in pregnancy may, of course, be only a symptom of a pathologic process in the liver or elsewhere. From the evidence we cannot conclude that bile retention itself predisposes to or causes miscarriage.

No data are available on the effect of jaundice on menstruation and conception. This would be an interesting field for observation.

The development of the ovary is stimulated by bile, according to Chinomiya (1948, cited); and the development of the testes is retarded in young experimental animals, as was shown by the daily injection for 19 days of 20 mg. of sodium taurocholate, which Chinomiya thinks contains an antimusculin substance.

Thelykinin, an oestrus-inducing hormone, has been found in commercial sodium taurocholate and fresh human bile, by Gsell-Busse. This action is not inherent in bile salts, according to the work of Haterius on spayed adult female rats, and 30-day-old female rats. He used subcutaneous injections of commercial sodium taurocholate (Eastman²) and sodium glycocholate (Merck²). The action of estrogen (Parke, Davis and Company²) was neither inhibited nor accelerated by subcutaneous injections of sodium taurocholate. The effect of bile acids on the permeability of the placenta was studied by Nattan-Larrier. A heteroserum given intracardially to guinea-pigs and rabbits did not pass into the fetus; but when bile salts were injected, followed in 10 minutes or longer by a similar injection of horse serum, the fetal blood contained the heteroserum. Sodium taurocholate and sodium glycocholate were equally effective.

² Manufacturers.

CHAPTER XVII

ACTION OF BILE ON THE GASTRO- INTESTINAL SYSTEM

AFTER bile enters the intestine, a portion of it is normally absorbed and some of it excreted in the feces. Under certain conditions, such as diarrhea, a larger portion is expelled in the stool. Bile is entering the intestine almost continuously, even during a fast of from 15 to 30 days by man and 60 days by dog (Carlson). (18)

The action of bile in the intestine on intestinal motility has been the subject of much irregular investigation. It is practically impossible, in experimental work, to simulate the normal application of bile to the intestinal mucosa. Bile is normally introduced continuously into the intestine of most animals, with periodic increases along with the passage of food from the stomach, so that the semiliquid gastric contents are immediately mixed with the duodenal juice, pancreatic juice, and bile, making a rather complicated but normal mixture of the four fluids. In some animals that do not have gallbladders, there is supposedly a more or less continuous passage of bile into the intestine. Most of these animals are herbivores, and the propulsion of food from the compound upper digestive tract is less intermittent than in the carnivores.

Certain methods used by various investigators for determining the action of bile on the intestinal motility are very questionable. The cut-strip method is certainly abnormal, because the animal is killed, the intestine removed, and either a longitudinal or circular strip is cut. Cut edges, serosa, and mucosa are all exposed to the effect of bile, which acts on all cells and certainly neglects none in these experiments. Normally bile comes in contact only with mucosa. Also, the ex-

trinsic nerve supply is cut off. When a whole section of the intestine is immersed in a water bath, bile comes into contact with the serosa rather than the mucosa. Furthermore, changes of a fraction of a degree of temperature cause marked changes in the muscular activity, and changes in the oxygen content of the water make serious variations in the records.

The method of checking expulsion time by the use of beads or pellets seems fairly accurate; but the method of giving bile by mouth in large quantities is unsatisfactory because it creates an unnatural condition, as the bile then must pass through the stomach before reaching the intestine. Keratin-coated bile pills are unsatisfactory, since the bile becomes active only after the keratin is dissolved at some indeterminate and uncertain interval of time and at an uncertain position in the intestinal tract. All feeding experiments must bear this criticism. The use of the fistula or loop method, in which balloons are used, is also criticized because the normal intestinal segment becomes active as soon as it is distended by its contents; thus the balloon itself is considered a stimulating agent.

The effect of bile given intravenously on the motility of the gastrointestinal tract is considerably more questionable.

The earliest mention of bile, in a sacerdotal papyrus written about 1300 B.C. and translated by Erman and Krebs,² is for the use of ox bile in prescriptions for enemas. In 1682 Greulichio commented: "Bilis est instrumentum plurimum,

² (511): "(1) Ein Gutes Mittel zum Kühlen

Ochsengalle 1/3

Kuhmilch 1/3

Frisches Baumöl 1-1/3

Honig 1/3

In den After spritzen, an 4 Tagen.

(2) Ochsengalle 1/3

Kuhmilch 5/6

In den After spritzen, an 4 Tagen.

Es ist gut.

(3) Äussere Leiden sind es mit denen sich die Recepte.

Ein anderes, um die Krankheit aus dem Bein zu vertreiben.

Kälbergalle

Fischgalle

Damit-salben."

Evacuationum, ac primo quidem catarrheos sive alvi movendae."

STOMACH

Ordinarily, we do not think of bile as being in the stomach, though Carlson believes that at times bile in the stomach is normal. An excess of bile in the stomach, however, causes vomiting, as was observed by Bouisson in 1841, when he gave by mouth 120 cc. of bile to a dog. In order to observe the effects, he prevented vomiting by tying the mouth and nose. ^(A) The dog then soon became weary and downcast.² Bouisson was the first to point out the probable relation of bile in the stomach to a "bilious nature." Bile was fed to rabbits by Leyden in 1861, and the animals died on the seventh day. Nothing abnormal was found at necropsy. Loss of appetite in a dog was caused by the feeding of 2 gm. of sodium *choleini-cum* in sausage by Naunyn in 1868.

The evacuation time of the stomach of man and cat was greatly diminished by 1 gm. of sodium taurocholate given by stomach tube. These observations were made with the Roentgen ray, by Pannett and Wilson. However, in choledochogastrostomy of four years' duration, there was no evidence of untoward effects of bile in the stomach (Mastroiommone).

Bile pills containing a total of 25 gm. of bile were fed to each of a number of chickens for 3 days by Rywosch (1659) in 1891. This was followed by diarrhea and by death on the fourth day. At autopsy the mucous membrane of the crops of the chickens showed traces of necrosis, and death was attributed to the direct inflammatory action of the bile. Thus it was pointed out that large quantities of bile acted harmfully in the stomach and intestinal tract and caused death. Small quantities of bile given by way of the stomach caused the appetite to decrease and diarrhea to increase. Rywosch further observed that 50 cc. of a 10 per cent solution of ox bile, when given to rabbits in the course of 3 days, caused

* "Traurig und niedergeschlagen."

marked inflammation of the stomach and death of all within 4 days.

A man with obstructive jaundice, according to Simnitzky, had a hyperacidity of the gastric juice, owing to an increase in free hydrochloric acid. The gastric-fluid quantity and concentration were increased. Following release of the obstruction, the gastric secretion returned to normal. A short time later, when a second obstruction developed, there was a return of the hyperacidity and again an increase in the gastric secretory function, which was in proportion to the intensity of the jaundice. This procedure is supported by the observation of Pannett and Wilson that gastric acidity increases more rapidly and ultimately reaches a higher level following the intake of food during jaundice.

Further research should be done on all of these problems.

Gastric motility of the hunger type was immediately but temporarily inhibited by intravenous injection of $\frac{1}{8}$ – $\frac{1}{2}$ cc. of gallbladder bile per kilogram of body weight in dogs by Still and Carlson. The gastric secretion following a test meal was greatly diminished by intravenous bile. However, the inhibitory effect on gastric secretion was more prolonged than on gastric motility. Fowls were fed sodium taurocholate and sodium glycocholate, by Hosono, causing the gastric secretion to be greatly diminished. Chronic obstructive jaundice is followed by a decrease of the motor activity of the empty stomach, a decreased rate of gastric juice secretion, and an increased acidity of the gastric juice.

Alcoholic extracts of bile were fed to 18 rats by Cooper in 1923. Most of the rats died within 48 hours, all being dead by the seventh day. At necropsy the intestines and stomachs were hemorrhagic, and there were erosions in the gastric mucosa in 3 rats.

SMALL INTESTINE

A Vella fistula was used by Fubini and Luzzati in 1888 to determine the action of bile on the small intestine. The passage of a pea through a loop of intestine was timed, and it

was found to pass through the lumen more rapidly after bile had been injected into the lumen than before. Bile in great measure promotes the peristaltic movements of the intestine.

The intestine of the living rabbit was immersed in a physiologic salt-solution bath by Eckhard to determine the effect of bile on the intestine. After injecting 1 cc. of rabbit bile into the duodenum, the intestine was absolutely quiet for 10 minutes. The injection of 3 cc. into other parts of the small intestine was followed by periods of inactivity, lasting from 15 to 20 minutes. Larger quantities of bile, likewise injected, resulted in wavelike movements along the intestine; but Eckhard believed this activity to be due to the mechanical stimulation caused by the bulk of the fluid.

The duodenum of the narcotized dog was studied, by Hallion and Nepper, by introducing a balloon through an opening in the intestine. Thiry-Vella fistulas were also used for the jejunum and ileum. Intravenous injections of ox bile in 3-cc. and 7-cc. amounts were made before and after tying off the common bile duct. Before tying off the duct, the injection produced gradual dilation of the intestine, followed by gradual amplification of contractions and increase of tone. When the duct was tied, the injection produced no effect. Immediately following intraduodenal injection of bile, there was a lowering of tone and a decrease of peristalsis; then the tone began to rise; and finally, after 29 minutes, the contractions were markedly augmented. The similarity between these last-mentioned results and those after intravenous injection was explained on the basis of the cholagogue action of bile in the blood stream. The increased secretion induced in the liver was poured into the duodenum, causing greater intestinal activity. Hallion and Nepper concluded that bile in contact with the intestinal mucosa has a local stimulating influence on the small intestine, especially upon the duodenum.

A Vella fistula of a cat's small intestine was used by Schüpbach for determining the speed of a pellet. Bile had no

special influence on intestinal loops except an important, though distinct, restraint on the activity. In experiments on the intestine in situ, with the animal under morphine-ether anesthesia, the abdomen was opened and bile was permitted to trickle onto the vigorously moving small intestine.³ There was immediate cessation of movement. Contractions of the surviving intestine, suspended either in Ringer's solution or in blood, were arrested when bile was introduced into the suspension liquid.⁴ The jejunum showed increased peristalsis following intravenous injection of bile, as shown by Ott and Scott, who used the balloon method. A weakening of activity and a decrease in the number of contractions of the small intestine by the strip method of Magnus was observed by D'Errico. The same results were obtained with sodium glycocholate and sodium taurocholate.

An extensive investigation of the action of bile on the entire intestinal tract has been made by Horrall and associates, Drs. Smiley, Regan, and Templeton. This extensive work has not previously been reported. The experiments were performed by the balloon method on unanesthetized dogs after recovery from operations making various kinds of intestinal fistulas: Thiry-Vella, Vella, double Thiry-Vella, and enterostomy at various sites, including cecostomy. The dogs were not fed for 10 hours preceding an experiment. Dogs were trained to lie still on a comfortable pad throughout the experiments and were fed at the end of each series of experiments. One dog, used every day for more than a month, could be trusted to trot unleashed from her cage to the laboratory. Upon arriving there, she jumped upon the table and lay down of her own accord, ready to be blindfolded and to have the balloons inserted. The influences of fright and pain were entirely eliminated. Dogs that could not be trained to feel at ease were not used. Special mechanical devices and special operative technic were used to prevent leakage of the intes-

³ Action of bile on the serosa, not the mucosa.

⁴ Same objection applies to both experiments.

tinal contents when the dogs were not being used for experimentation. The animals remained in otherwise normal condition throughout the entire time they were used. The intestinal contractions were recorded on smoked drums by the use of multiple tandem balloons, Templeton method, placed in the intestines and connected by rubber tubes to manometers.

The following substances were used in the investigations: dog hepatic bile; ox, dog, pig, and human gallbladder bile; human fistula bile; sodium glycocholate, taurocholate, cholate, and dehydrocholate. The control solutions employed were: water, physiologic salt solution, dog gastric juice, pancreatic juice, and a few foods.

The most significant characteristics of the series of tracings for this investigation were: the average height of contractions, the average tonus following injection into the gut lumen, and the duration of the altered activity. These were tabulated for each tracing for the control periods, for the period of activity immediately following injection into the gut lumen, and for what we have called the period of "remote gut activity." Duration of the immediate gut activity was considered as that time during which there was a distinct change from the tonus and average height of contraction during the control period. The remote activity was considered as that which followed, for a variable time, the immediate activity. In a large percentage of cases it was distinctly different from both the control and the immediate effect in tonus and height of contractions.

Gallbladder bile of the ox, injected into the duodenum, produced a curve of increased activity very similar to that of sodium glycocholate and dog gallbladder bile.

A period of relaxation frequently preceded the stimulation produced by the injection of one of these substances. In 45 per cent of the instances in which sodium glycocholate and dog gallbladder bile were injected, this dilatation of the gut was indicated by one or all three of the balloons. Dilatation

occurred in 28 per cent of the injections of dog gastric juice and in 9 per cent of the injections of physiologic salt solution. The large proportion of instances following the injection of bile or bile salt, causing a primary dilatation before the stimulation, would indicate that these substances have a definite relation to this particular action of the gut.

It was observed in 21 control injections of physiologic salt solution that at body temperature the injection of 4 cc. in 45 seconds caused no change in the tonus, average height, or rate of contractions occurring. Constant temperature, quantity, and rate were used for the greatest part of these investigations.

In four experiments on duodenal fistula dogs it was found that, if the dog had been fed within 6 hours, the gut was in such high tone and so highly active that the injection of any of the substances being studied produced little, if any, effect. During these experiments intestinal contents streamed from the fistula in intermittent gushes.

Experiments on dogs with both duodenal and gallbladder fistulas with tandem balloons inserted in the intestines toward the pylorus demonstrated that sodium glycocholate injected into the gallbladder caused the emptying of that organ with increased intestinal activity similar to that resulting from the injection of bile into the gut lumen by way of a tube.

Four tracings were made on duodenal fistula dogs from $\frac{1}{2}$ to 2 hours after feeding a small quantity of milk or cream. In three of these experiments, increased activity was coincident with the flow of bile-colored fluid from the fistula. The fourth experiment showed a very active gut, which relaxed for about 1 minute following each flow of bile-colored material from the fistula. Considering the last-mentioned experiment an expression of the same sort of activity as was demonstrated in the first three, but presented in a different time phase, the evidence here would indicate that bile flowing into the intestine normally causes an increase in activity. The results of similar experiments by Hallion and Nepper

lend some strength to the evidence that bile from the liver flowing into the duodenum—during digestion, for instance—may cause an increased activity of the gut.

RÉSUMÉ

From the various results set forth above, it is indicated that bile has the particular characteristic of stimulating gut activity. Bile and bile salts acting through their natural channel, the intestinal mucosa, have a temporary local stimulating effect on the motility of the small intestine.

COLON

Diarrhea was observed incidentally, by Whipple and Smith (2096), in dogs to which large quantities of bile, 21 gm., had been given by mouth. They say that there is no quantitative test for the bile salts in the feces.

The amount of bile passed in the feces of a dog weighing 8 kg. was estimated by Bidder and Schmidt. The solids of the bile passed in 5 days weighed 38.52 gm. The feces contained only small traces of bile. The bile of these dogs contained 6 per cent sulphur. If all the sulphur of the bile had been excreted in the feces, it would have amounted to 2.37 gm.; but only 0.334 gm. of sulphur was found, and so it was evident that very little of the taurocholic acid which passed into the intestinal tract was excreted therefrom.

There have been various arguments as to what becomes of the bile after it has been thrown into the intestinal tract. The consensus of opinion at the present time is that some of the substances, such as bile acids and possibly some of the pigments, are reabsorbed and conserved, while other substances, such as cholesterol, are purely excretory products.

Bile acids given by mouth caused an increased Pettenkofer reaction of the blood from the portal vein, but the Pettenkofer test of the blood in the peripheral circulation was not affected (Rowntree, Greene, and Aldrich), although these bile acids were quickly recovered in the bile by way of a biliary fistula. Bile acids in the portal blood were increased,

two to three times, 15 minutes after bile salts were injected into the duodenum, according to Greene, Aldrich, and Rown-tree (715).

Bile diarrhea, according to Wagner (2028), is due to a pathologically increased liver activity, which causes the excretion of excess bile into the intestine. Broun, McMaster, and Rous (269) observed that bile in sufficient quantity given by mouth often acted as a purgative and, in consequence, may itself be so rapidly hurried through the bowels as to appear unchanged in the stool. This took place in several of the experimental animals. Röhrig also injected bile salts per rectum, following which he observed a slow pulse and other toxic symptoms followed by death. The action of bile salts injected into the rectum was as rapid as bile injected intravenously. Injections of bile acids in 10 per cent solution into the rectum of rabbits were followed by diarrhea (Leyden [1105]). The absorption of the bile acids by the lower portion of the large intestine was proved by the finding of bile acids in the urine of the injected rabbits.

Following intravenous injection of bile acids, Feltz and Ritter (566, p. 576) observed the animals licking their lips as if something disagreeable was in their mouths. The present writer has also observed this very frequently following the intravenous injection of bile or bile acids, and, in addition, has usually found that the animals become very thirsty almost immediately following the injection. Legg (1082, p. 193) suggests that the reaction in these animals is due to a possible "presence of the bitter bile acid salts in the blood." Many workers have observed marked increase in secretions, especially in salivary and nasal secretions following the injections of the bile acids.

Schüpbach, Hallion and Nepper, D'Errico, Berti and Bernucci, and many others discussed the question as to whether the action of bile is on the nerve or on the muscle of the intestinal tract.

Some cases of diarrhea initiated by a foreign substance,

even though this substance has been removed by the diarrhea itself, are found to continue. Just what action is present is difficult to determine. It may be that an irritated muscle is slow to return to normal; it may be that bile, the absorption of which is interfered with by the initial diarrhea, is carried the entire length of the intestine, now causing the continuation of the diarrhea. In the latter case the enterohepatic circulation is abolished, or at least diminished. Not only the effect of increased and prolonged action of bile, and particularly bile salts, on the intestinal tract but also the effect of their absence or diminution on the entire organism is here evident.

The effect of bile on the colon was recently studied by Templeton on five dogs with six tandem balloons connected with six recording manometers. By this series of balloons the immediate and remote effect of injections could be observed. Bile and bile salts were injected at various levels of the colon, and accordingly the balloons at the different levels recorded the motility. He found that the enema most likely to produce evacuation was not necessarily the one which increased the colon activity, as is generally believed. The effect of the enemas may be to produce relaxation rather than contraction. Intracolonic injections of bile produced a marked relaxation of the colon; on the other hand, oil caused increased contraction. However, on the other hand, bile was more effective in producing an evacuation, and oil the least effective. He believed that a relaxed or quiet colon might indicate an urge to defecate.

By using three tandem balloons, Horrall found that the intracolonic injection of bile caused relaxation immediately but that this was followed by vigorous contractions. He used colostomies at several different levels in dogs. All observations were made without anesthesia. The peristaltic waves in the caecum were the reverse of those in the rest of the colon. The reactions of the different dogs varied considerably in intensity and length of time of action.

Bile is apparently necessary in the intestinal tract for normal bowel movements. Constipation is the rule in patients with jaundice. Where all the bile has been excluded from the intestine for a few weeks, cathartics are usually necessary. The relation of bile to diarrhea has not been definitely determined.

PEPTIC ULCERS

Some recent research has been directed toward the relation of bile to peptic ulcer. Subcutaneous and intraperitoneal injections of bile have been the cause of gastric ulcers, according to Sellards (1742). Five per cent sodium glycocholate in doses of 0.03 gm. was injected daily into the guinea-pigs. Ulcers appeared in 4 out of 7 animals after 2 or 3 days. The rabbits were injected intraperitoneally with 4 cc. the first and second days and 7 cc. the sixth day. Numerous lesions were found in the gastric mucosa, and there was also evidence of old hemorrhage. He questioned whether the mechanism of the production of peptic ulcer was initiated by the hemorrhage which is common in jaundice or whether it was due to anaphylaxis.

External biliary fistula and obstruction of the common duct cause multiple gastric and duodenal erosions (Berg and Jobling, and Bollman and Mann [209]). In contrast to this, obstruction of the pancreatic duct does not cause ulcers (Berg and Jobling), but external pancreatic fistula does. Elman and Hartmann observed ulcers in 6 dogs with total external pancreatic fistulas of 13 or more days' duration. They suspected the high acidity of the stomach, with failure of the juice to neutralize it, as being the cause of the ulcer.

As previously mentioned, hyperemia and necrosis of the mucosa of the crops of chickens and stomachs of rabbits follow the feeding of large amounts of bile (Rywoch). Gastric hemorrhage follows the feeding of sodium taurocholate and sodium glycocholate (Hosano). Ox bile fed to dogs and bile diverted into the stomach by way of cholecystogastrostomy cause no disorder in the gastric mucosa of the animal (Oddi).

A number of workers have diverted bile through the gallbladder or common duct into the stomach in experimental animals; and surgeons have repeated this work in man many times, without ill effects. It would appear, particularly from work on man, that the stomach is damaged very little, if at all, by the ordinary amount of bile.

Bile was diverted by Smith (1784) into the stomach of 12 dogs, and no disturbance was observed; but when an excess of hydrochloric acid was added to the stomach, hemorrhagic areas and small ulcers appeared. Bile introduced into the stomach of a cat or dog in the presence of 0.5 per cent hydrochloric acid caused erosions of the mucosa in 28 of 40 animals. Bile confined in the stomach in the presence of 0.5 hydrochloric acid caused necrosis of the epithelium and hemorrhage in the mucous membrane, with resultant superficial ulcers. The action of bile-hydrochloric-acid mixture is much more toxic to the gastric epithelium than either bile or acid alone. The power of bile acids to produce gastric ulcers is increased by additional feeding of thyroxin to guinea-pigs and is inhibited by the feeding of lecithin (Schmidt). Feeding the thyroid with bile salts induces ulceration (Trincas). Cholesteryl oleate is antagonistic to bile salts in gastric-ulcer formations (Ishii).

Duodenal ulcers were found by Kapsinow in 17 of 43 dogs with complete external biliary fistula of more than 2 weeks' duration. The bile was drained through an anastomosis of the gallbladder with the pelvis of the kidney. Similar ulcers were described by Berg and Jobling in 13 of 23 dogs with total bile exclusions from the duodenum. The exclusion was produced by complete obstruction of the common bile duct or by drainage to the outside. They suggested that mucus in the bile is the protective component, and that, by covering the surface epithelium, it prevents the action of gastric juice on the epithelium.

It is rather interesting to observe the protective action of bile against gastric ulcer. In 14 dogs bile was diverted into

the stomach, and in 8 other dogs pancreatic juice was likewise diverted. Of each group, ulcers developed in 5 dogs after gastrojejunostomy (Graves [706]). Hence pancreatic juice is more likely to cause ulcer than bile.

Obstructive jaundice was produced by Bollman and Mann (209) in dogs by double ligation and section of the common duct; at the same time they removed one to three lobes of the liver. At autopsy 64 animals that had survived from 5 to 295 days showed peptic ulcers; 23 dogs living from 21 to 195 days did not show ulcers. The ulcers were located at various places in the stomach and duodenum. The most common cause of death of these jaundiced animals was perforation of the ulcer with resulting peritonitis; the next was hemorrhage into the gastrointestinal tract. Bile by mouth had no preventative action. Bollman and Mann did not offer any explanation as to the mechanism involved; nor were they willing to draw a parallelism with man.

Glycerol and cholesterol, according to Tashiro and Oliver, had no antagonistic action on bile salts and did not inhibit the ulcer-forming power of the bile salts. Tsuruta repeated the work of Sellards and then added to the bile, before injection, stearic acid, crude phosphatides, lecithin, and cholesteryl oleate, and found that these protected against the formation of peptic ulcer.

The present writer is unable to find any direct clinical relationship between ulcer and jaundice. Ulcers do not occur in dogs with jaundice due to ligation of the common duct unless these ulcers occur very late in the course of the disease. The malnourished animals have general cachexia, and there is no effort of repair about the edges of the ulcer. These ulcerations probably occur after the dogs become moribund. Since the gallbladder is able to protect itself by a very slight acid secretion, it is improbable that the entering of bile into the stomach, which secretes a relatively large amount of acid, should cause ulcer.

Following fatal intraperitoneal or intravenous injection of

bile into dogs, the writer has frequently seen numerous small hemorrhagic areas in the intestinal tract, few in the stomach, many in the small intestine, and few in the large intestine. These hemorrhagic spots varied in size from pin point to 2 or 3 mm. in diameter; and if the dog remained moribund for a few days, sloughs appeared. It may be presumed that intravenous bile causes disintegration of the capillary wall or increases its permeability, so that there could be a small hemorrhage; or that the bile which was absorbed from the peritoneal cavity and that given intravenously cause small emboli, which lodge in the arterioles and produce the hemorrhage; or that the blood is so altered that it passes more easily through the blood-vessel wall. Increased coagulation time in jaundice is a possible factor in causing ulcers by permitting hemorrhage with subsequent necrosis. It is uncertain whether bile causes the ulcer directly or indirectly. Why the subcutaneous or intraperitoneal injection of bile, or the obstruction of the common duct, or external biliary fistula would also cause peptic ulcers is certainly not evident. The protective power of the bile in the stomach by regurgitation or in the duodenum as a neutralizing agent of the gastric acid has been suggested. Thus, the absence of bile, with its subsequent marked cachexia rather than its presence, would be regarded as the cause of peptic ulcer. The feeding of bile to animals having ulcers with cachexia from biliary fistula causes the ulcers to heal or even prevents their formation (Blanck). The prevention of ulcer or its healing is related to the general normal nutrition produced by the normal amount of bile.

INTESTINAL OBSTRUCTION

The relation of bile to the intoxication in intestinal obstruction has been questioned, but adequate experimental evidence either for or against it is lacking. It is well known that the higher obstruction is much more toxic than the lower, and that bile is much more concentrated in the upper

gut than in the lower; but the exact relation has not been determined. Serious toxemia may be entirely independent of bile. Bile may even be beneficial, acting as an inhibiting agent on the toxic pancreatic juice, as suggested by Saito.

The recent work of Benedict, Stewart, and Cutner offer evidence that bile is beneficial in obstruction.

The recent discovery of *Bacillus welchii* in the vomitus in intestinal obstruction, the development of a culture media in the intestines by the obstruction, and the observations that, when bile is injected into the peritoneum, *B. welchii* develop very rapidly may offer new channels for research.

The role of bile in intestinal obstruction needs investigation.

CHAPTER XVIII

ACTION OF BILE ON BACTERIA AND TOXINS

ANTISEPTIC properties have been attributed to bile, mainly because of the augmentation of the putrid odor of feces and gas caused by the absence of bile from the intestine in obstructive jaundice. The feces are decolorized and contain much fat, indicating the absence of bile. The pollution is attributed to intestinal bacteria which grow in the absence of bile; from this it can be deduced that bile either kills bacteria or prevents their growth, according to Saunders, Tiedemann and Gmelin, and von Gorup-Besanez.

Meat and albumin were put into solutions of bile acids by von Gorup-Besanez (2014) in 1846. The mixture was kept for 48 hours at body temperature. At the end of this time there was no trace of putrefaction. The control tubes containing meat or albumin and plain water, treated in the same way, gave very distinct signs of putrefaction in 24 hours. Bile delayed fermentation of syrup solution, urine, and the like.

The absence of bile from the intestine results in the failure to absorb fats, and a large amount of fat prevents digestion of the protein because of the fat envelope about the protein masses. This permits the activity of putrefactive bacteria under cover of the fat incasement, thus producing putrefactive products and odors. Bile, for these reasons, has been called an "antiseptic."

Bacteria passes through the intestinal wall in acute intestinal obstruction, according to McClure. Was the weakening of the intestinal wall caused by bile?

Stolnikoff placed in bottles: (1) bile and water; (2) fibrin,

bile, and water; (3) fibrin, fat, and water; and (4) fibrin, fat, bile, and water. The gases given off were collected over mercury for 2 months. Number 1 gave off no gas; No. 3 gave off the most gas, which was 92 per cent carbonic acid. The contents of the bottles were then analyzed and were found to contain cholic acid, taurin, and glycocholl. From this Stolnikoff concluded that the bile acids may delay putrefaction but do not prevent it entirely, as even the bile and water solution contain new split products. He also concluded that the function of bile is not to prevent putrefaction in the intestine but to increase intestinal absorption.

An examination of gallbladder bile for bacteria and experimental inoculations of sterile bile with bacteria should give new information on this subject. Some bacteria are killed by bile and bile salts, while other bacteria grow, such as typhoid and typhus, depending on the pH (Schultz-Brauns). Koch's cholera bacillus, spirillum from Indian cultures, and Eberth's and Ribbert's bacilli all grow vigorously in sterile ox-bile inoculations (Sherrington [384, cited]).

Gallbladder bile and gallbladders were obtained at operations and examined bacteriologically by Mestitz and Ritter in 1928. Of 80 cases, 33 (41.25 per cent) were sterile. *Bacillus coli* was present in 16 cases, 5 times with other germs. *Staphylococci* were present in 15 cases: *S. albus*, 12 cases; and *S. aureus*, 3 cases. *Streptococci* were present in 12 cases. *Bacillus typhosus*, *B. paratyphosus*, *B. lactis aërogenes*, and *B. faecalis alcaligenes* were each present in 1 case. Bacteria were present in the bile in the gallbladder in 58 per cent of 735 cases operated on at Johns Hopkins Hospital and reported by Blalock. The postoperative diagnosis was gallstones in 599 cases and cholecystitis in 136 cases. *Bacillus coli* was present in 49 per cent of these cases and *B. typhosus* in 19 per cent.

Gallbladders and gallbladder bile obtained at operation from 66 men and 352 women were examined by Schultze. Of these, 131 contained bacteria; 66 contained *B. coli*, *B. lactis*

aërogenes, and paracolon bacilli; 15, streptococci—mostly green; 9, *B. typhosus*; 5, *B. paratyphosus*; 11, *S. aureus*; 9 *S. albus*; 8, *B. proteus* and *B. fluorescens*; 7, mixed with *B. coli*; and 1, spore-former.

The human bile passages contain many bacteria, according to investigation of the contents removed at operation or by duodenal drainage. Thorsness found that, out of 75 gallbladders removed, 30 were sterile and that, out of 59 from which bile only was removed, 50 were sterile. Hanssen found that, in specimens obtained by cholecystectomy, 32.7 per cent were infected from duodenal drainage and 75 per cent showed mixed cultures. Nickel said that the majority of gallbladders removed at operation were infected. Lyon observed that only 16 per cent were sterile when bile was removed by duodenal tube.

Although many bacteria are killed by bile, in icterus, where there is a "supercharge" of bile, the patient is very prone to severe malignant infections. The bactericidal power of jaundiced blood may be lowered.

Bacillus anthracis, spirilla, *B. prodigiosus*, and cocci were isolated, by Copeman and Winston, from human bile obtained from a case with biliary fistula. Bile could not be regarded as an antiseptic agent in the strict sense of the term, although it doubtless had some effect in preventing putrefactive processes in the intestine. Bile favors the development of certain bacteria, such as *B. coli*, but inhibits the anaerobes (Lagane). The solubility of pneumococci in bile was detected by Neufeld. He attributed it to the bile acids. Mixtures of pneumococci cultures and bile were injected intravenously and subcutaneously, and all the animals lived. Smaller quantities of pneumococci without bile were injected in control animals, and all died. The bacteriolytic action of the soaps of unsaturated higher fatty acids isolated from ox bile has been demonstrated by Kozlowski. Pneumococci were dissolved in 1 hour by these soaps in solution of 1:50,000, whereas bile kills in 1:5,000 dilution.

According to Downie, Stent, and White, all normal strains of pneumococci are equally susceptible to the lytic action of bile salts. Of the rough strains, five are equally soluble, while one is completely resistant. No parallelism exists between lytic activity and surface tension of solutions of the various bile salts. Sodium dehydrocholate and sodium dehydrodesoxycholate do not cause lysis.

Since bile has a specific cytolytic power for pneumococci, several attempts have been made to use bile or bile salts in the treatment of pneumonia. Experimenting with white mice, Hilgermann injected intraperitoneally sufficient pneumococci and virulent streptococci to cause death in 48 hours. This injection was followed by the injection of dilute bile or bile salts subcutaneously. The mice receiving the injections of bacteria and bile lived; but the controls, receiving only bacteria, died. He concluded from animal experiments that the alkali of bile acids can be used for prophylactic purposes. This is not an example of internal disinfection.

Bile is lytic for virulent pneumococci, according to Reimann; but pneumococci adapt themselves to live and multiply in high concentrations of bile. After repeated growths in bile, pneumococci become less virulent. Bile salts accelerate the autolysis of live gonococci *in vitro* but have no effect on dead cocci (Price).

Increased alkalinity of the bile has a marked inhibiting effect on the bacterial action; thus, in bile that is strongly alkaline the bacteria are either destroyed or become latent. As soon as the bile is diluted, the alkalinity decreases and the bacteria become active (Beckmann). An attempt was made to alkalinize the bile in Rous fistula dog and in man with a postoperative biliary fistula; but sodium bicarbonate, given orally, according to Ottenberg and Kahn, had no effect on the pH of the bile. The liver eliminates bacteria from the general and portal circulations (Fütterer). Bacteria may be present in the bile for a considerable length of time and remain inactive until proper conditions for growth arrive, such

as a decrease in alkalinity of the media. Bacteria may get into the bile through the liver, walls of the bile ducts, or by ascending from the duodenum.

The old view was that the liver removed the bacteria from the body as an act of self-purification. The Kupffer cells were phagocytic and discharged the bacteria into the bile capillaries. *Bacillus pyocyaneus* was injected intravenously into 26 rabbits, and the bile from an ordinary fistula was sterile after an interval of 105 minutes in all instances. The heart blood was positive. But when there was liver damage due to ether, chloroform, urethan, or phosphorus, bacteria were found in the bile. The blocking of the endothelial system with India ink had no effect on the passing of bacteria from the blood to the bile. Popper concludes that the removal of bacteria is not a specific liver function but that the passing into the bile is due to a disturbance of the barrier.

Bacterium dysenteriae of Shiga has been cultured from human blood by the aid of 1-10 per cent sodium taurocholate by Pfannenstiel and Kortmann. In this instance small quantities of bile or bile salts not only did not inhibit bacterial growth but accelerated it in the blood cultures. Ox gall, full strength, inhibited the growth. Calalb stated that a small quantity of ox bile inhibits the action of the bacteriophage without destroying it. This action may explain the continued presence of typhoid bacilli in the gallbladder. *Bacillus typhosus* virus is attenuated by bile (Dimitrijević-Speth).

The endotoxins and exotoxins of *B. coli* were destroyed in vitro in a few hours by sterile beef bile (Vincent). A mixture of 3 cc. of ox bile and 200 lethal doses (for a guinea-pig) of tetanus toxin was injected into the peritoneal cavity of a rabbit without causing any ill effect. *Bacillus coli* toxin, 1.5 cc., given intravenously, killed a rabbit; but the same amount of toxin, plus 1.5 cc. of beef bile, given intravenously, had no effect. Subcutaneous injections caused abscesses. Vincent also pointed out that bile detoxifies the toxins of *B. coli* and *B.*

tetanus in vitro and in vivo. An immunity is obtained by repeated injections of a mixture of bile and bacterial toxins.

With the newer knowledge of the effect of bile on bacteria, particularly on *B. welchii*, we wonder if, in intestinal obstruction, bile in the upper intestine increases the permeability of the intestinal mucosa. The bile is more concentrated and in a freer state in the upper intestine than in the lower, and high intestinal obstruction is far more toxic than low obstruction.

Several types of bacterial growth are stimulated by the addition of bile, according to Meyerstein. It is clearly a nutritive medium without any additional substance needed for *B. pyocyaneus*. Bile is an excellent medium for *B. coli* if a small amount of other substances is added. A very small amount of bile in cultural media, however, inhibits the growth of *S. pyogenes aureus*. Eighteen different kinds of bacteria, including staphylococci, streptococci, *B. pyocyaneus*, *B. coli*, *B. typhosus*, *B. paratyphosus*, *A.* and *B.*, Flexner's bacilli, *B. aërogenes*, etc., all grew in 10 per cent and 70 per cent bile (Drennan at Mayo Clinic). In 19 per cent of gallbladders of man removed at operation the fluid content of the gallbladders contained bacteria.

The antiseptic action of bile in the animal body has not been definitely proved; some intestinal bacteria seem to thrive in bile. Intestinal putrefaction may occur because of the absence of the normal motility of the gut when normal bile salt stimulation of the tract is lacking. This stasis may give time for the putrefactive organisms to work on the proteins. On the other hand, the products of putrefaction seem to stimulate the intestine, causing diarrhea, bringing more bile downward. Occurrence of large amounts of indican and phenol in the urine in jaundice indicates an increased intestinal putrefaction.

Bile plays a definite role as a detoxifying agent, according to Hayakawa. Substances which are poisonous are rendered inert by the addition of bile. Certain poisons are destroyed. Organic poisons which are normally detoxified by the rabbit

are quantitatively less detoxified after the common duct is ligated. The active detoxifying substances in bile are the salts of cholic acid—sodium glycocholate, the most effective; then sodium taurocholate; and least active, sodium cholate. Bile has no effect on histamine, peptone, choline, homologous serums, hemolyzed blood, spoiled meat, tetradotoxin, cobra venom, and dysentery vaccine. Some organic poisons are not affected, while others are completely detoxified.

Bile does not destroy *B. typhosus* or *B. paratyphosus*, but acts more favorably on their development (Pancalos). A rabbit weighing 750 gm. was given an intraperitoneal injection of 5 cc. of a 24-hour culture and died in 12 hours. Bacilli were found in the peritoneum and in the heart blood. Another rabbit was given an intraperitoneal injection of the same number of typhoid bacteria, grown in bouillon, to which enough beef bile had been added to make a 25 per cent solution. It had no effect. Four days later 5 cc. of 24-hour culture were injected, and the animal died. Permanent immunity had not been established. In a third experiment the same bile typhoid cultures were used. Ten days later plain bouillon cultures were injected with no effect. Pancalos concluded that bile is not harmful or antiseptic to typhoid bacilli but has an antitoxic action which is very marked.

Small quantities of ox bile inhibit the lysant property of the bacteriophage without destroying it. This may explain the fact that in typhoid fever and in typhoid carriers the bacilli linger longest in the gallbladder (Calalb).

Ox bile and human bile interfere variously with different strains of bacteriophages but are less inhibitory than blood or serum. Bile inhibits the phage against *B. coli* and *B. typhosus* less than against streptococci and staphylococci (Applebaum and Patterson). Human bile was investigated for phages in 30 cases, and none was found. Ten per cent of the specimens were sterile (Kanzler).

Vaccine virus is partially destroyed, as concerns the production of skin pustules in rabbits; but the vaccination does

not confer decreased immunity (Courtois). Dysentery toxin, mixed with bile salts before injection, become very much less toxic for rabbits (Auguste).

RÉSUMÉ

Bile, under ordinary conditions, is sterile but is not bactericidal. This has been questioned by some investigators, but the pathogenicity of the organisms they recovered has not been proved under the conditions in which they are found. If this action of bile is not toxic, it is surely antagonistic.

CHAPTER XIX

BILE AND ACUTE PANCREATITIS

BILE injected into the pancreatic duct causes acute pancreatitis, according to Opie (1417). In an experiment the injection of 5 cc. of dog bile into the pancreatic duct of dogs caused death in 50 per cent of the dogs within 24 hours. A large number of case reports of death from acute pancreatitis have been cited in which, at autopsy, stones were found in the common duct near the orifice, obstructing the outflow of bile and easily diverting it into the pancreatic duct, with hemorrhage in the pancreas. Bile has been forced into the pancreatic duct by small gallstones lodged in the diverticulum of Vater, making a mixture of pancreatic juice and bile, which caused acute pancreatitis and death.

Experimental acute pancreatitis was produced by the injection of sterile bile into the pancreatic duct by Whipple and Cook. Edema and hemorrhage were evident within 5-10 minutes following the injection. They concluded that the extremely early intoxication is due to 'protein-split products. Spasm of the sphincter of Oddi diverts the bile into the pancreatic duct, according to Archibald. Acute pancreatitis was produced also by injecting bile into the duct of Wirsung in dogs, causing death in 24-48 hours (Brocq and Morel). Necropsy revealed an effusion of blood in the abdominal cavity, hematoma of the pancreas, and patches of fat necrosis in the pancreas and greater omentum.

This work was repeated with goats by Mann and Giordano. Bile was injected into the pancreatic ducts of 3 goats without producing acute pancreatitis, although there was a slight local necrosis. The common duct in 5 goats was ligated without causing acute pancreatitis. The anatomy of the goat's pancreatic duct in its relationship to the common duct is such

that a ligature could be placed well above the ampulla, making a continuous connection of the pancreatic and bile ducts. They also examined the relation of the bile and pancreatic ducts to each other in 200 human specimens. In only 3.5 per cent of the cases was it possible to obstruct the exit of the ampulla and cause bile to pass into the pancreatic duct. They concluded that injection or reflux of bile into the pancreatic ducts could not have caused acute pancreatitis in man.

It is indeed fortunate that acute pancreatitis does not occur in more than 3.5 per cent of the people, as the mortality rate is extremely high.

A study was made by Cameron and Noble to determine whether water would flow up the duct of Wirsung when the ampulla of Vater was blocked, and, if so, at what pressure. A biliary calculus was artificially impacted in the ampulla of Vater; a reservoir of water which could be raised was connected with a manometer and the hepatic duct. In 65 per cent of 100 consecutive examinations of bodies at autopsy, water was forced up the pancreatic duct when a stone blocked the ampulla. A pressure of less than 100 mm. of water was used. This is in striking contrast to Judd's conclusion that this is possible only in 4.5 per cent in 170 cases, and Mann and Giordano's 3.5 per cent in 200 cases.

The etiology of acute pancreatitis was reviewed by Wolfer (2142), and the collected evidence suggested that bile is not the whole cause of this disease. In Wolfer's more recent work, he concluded that the entrance of pancreatic juice into the hepatic duct or gallbladder is frequently the cause of acute cholecystitis, probably due to the mixture of bile and pancreatic juice.

Experimental evidence was presented by Dragstedt, Hammond, and Ellis, indicating that the secretion pressure in the pancreatic duct is greater than in the bile duct. Other factors make it possible for bile to enter the pancreatic duct. The mixture of pure bile and pancreatic juice alone do not cause activation of the enzymes, but necrosis of pancreatic tissue

by bile and the advent of bacteria institute the acute symptoms.

The pancreatic ferment, trypsinogen, is inactive. It is normally changed to trypsin in the intestine, but can be activated by various substances. This activation is accelerated by the bile acids. The injection of activated trypsinogen into the pancreatic duct causes acute pancreatitis, but the injection of inactivated trypsinogen does not produce harmful effects.

Recent work by Wangensteen (2049) proved that acute pancreatitis regularly results from the injection of bile into the pancreatic duct. Various types of aseptic operations were performed to cause a reflux of bile into the pancreas, using 289 cats and dogs. Ligation at the ampulla in 131 animals was done to establish a common channel between the bile and pancreatic ducts. Positive gross changes were observed in 52 of these animals. Bile was injected into the pancreatic duct following ligation in 5 animals; all developed positive microscopic and gross changes. Of 89 animals with infections of the gallbladder after the various types of operations, positive microscopic changes of acute pancreatitis were found in 10. Injection of bile into the pancreatic gland in 32 animals resulted in positive microscopic changes of pancreatic necrosis in 13 animals. Trauma alone in 30 animals resulted in microscopic changes of acute pancreatitis in only 1 animal. Wangensteen concluded that the retrojection of bile into the pancreatic duct under the influence of contraction of the gallbladder produces pancreatic necrosis with a fair degree of regularity.

Considerable experimental work has proved that, when bile is mixed with pancreatic juice in the pancreatic duct, acute necrosis usually results. It has been suggested that bile interacts with the mucous membrane lining the bile ducts and that the mixture of bile and tissue juices activates pancreatic enzymes. The pancreatic enzymes in the duct of Wirsung are already activated; and when they come into contact with

bile, the speed of activity is increased, thus changing a negligible activity to a greater activity. If bacteria are present in the bile, the speed of action of the pancreatic juice is greatly accelerated. By their alkalinity, the bile salts furnish favorable media for the action of the pancreatic enzymes.

The conception of a possible relationship of acute hemorrhagic pancreatitis to the influx of bile into the duct of Wirsung has caused many surgeons to drain the bile passages in cases of pancreatitis.

RÉSUMÉ

✓ Bile can cause acute pancreatitis.

CHAPTER XX

WHY BILE DOES NOT CAUSE NECROSIS OF THE GALLBLADDER

BILE is very toxic to all the body tissues, especially when the salts are concentrated. The bile in the gallbladder is from five to twenty times more concentrated than that in the hepatic duct. Not all the substances are concentrated to the same degree. Some are absorbed; others are concentrated proportionally to the removed water; and some are added by the gallbladder mucosa. The bilirubin and bile salts are probably concentrated in proportion to the water. A stronger alkali or acid acts more rapidly on the tissues.

The liver bile was alkaline, as shown by vital staining (Rous [1633]). Since cresol red in liver bile gave a red color, the pH was greater than 7.4; and since thymol blue gave a yellow, the pH was less than 8.4. As the bile passed into the gallbladder and was concentrated, the alkalinity diminished, causing the pH to return to the normal or slightly acid state. In the center of the bile in the gallbladder the pH was 6.4; but about the periphery it was lower, so that bromcresol purple gave a greenish-yellow color with a pH of 5.4. Adjacent to the gallbladder mucosa or in the folds the pH was below 5.4, as the same dye gave a yellow color there. The wall of the gallbladder was also slightly acid in spite of the fact that it consisted largely of connective tissue. It came in contact with stored alkaline bile and removed constituents that were predominately alkaline in character. The tests were made in mice by Rous, using intraperitoneal injections of 1 per cent solution of dyes. In vivo observations were made after permitting time for absorption, which was from 2 to 4 hours. Bromcresol purple was purple when the pH was

6.4-6.6 and yellow when the pH was 5.4; gallbladder bile was very purple to black; gallbladder wall, yellow to green; liver bile, purple microscopically; hepatic parenchyma, yellow-green. Chlorophenol red showed: gallbladder bile, rose-purple, pH 6.24; bile in folds of mucosa, orange, pH 5.59; gallbladder wall, purple to yellow; liver parenchyma, pale yellow, pH 5.29; bile in the ducts, rosy, above pH 5.91. Other dyes showed corresponding results.

The vital staining showed that the bile itself was strongly alkaline in the gallbladder. About its margins it was considerably less alkaline, and near the gallbladder wall the bile had a slightly acid reaction. The wall of the gallbladder was acid; the liver parenchyma was acid; bile in smaller hepatic ducts was slightly acid; and bile in larger hepatic ducts was alkaline.

The bile of the dog had a pH of 5.66-7.84 normally. This could be increased to 8.3 or 9.0 by provocation with histamine (Carnot [1592, cited]).

The wall of the gallbladder and bile passages has a very marked capacity to reduce the strongly alkaline bile. The protective substances which occur in the bile are cholesterol, lecithin, fats, and proteins. These substances actually diminish the cytolytic activity of the bile salts. Mucin is added by the lining of the bile ducts and gallbladder. This acts in two ways: first, as a mechanical protective covering for the mucosa; and second, as a chemical neutralizer of the bile salts. Both the true and pseudo-mucins are very soluble in alkalies such as bile salts.

RÉSUMÉ

It would seem that the acidity of the living liver cells and gallbladder mucosa protect themselves against strongly necrotic alkaline bile by throwing out enough acid to make a zone of neutrality between the living cells and the bile.

CHAPTER XXI

BILE PERITONITIS

BILE PERITONITIS is a peritonitis caused by the chemical action of bile on the peritoneum. *Biliary peritonitis* is a peritonitis caused by bacteria in the presence of bile. These two conditions are frequently confused. In the first it is necessary that a sufficient quantity of bile acids be present. In the second pathogenic bacteria are essential but bile acids are not. In order to complete the delusion bile pigment is indispensable, it gives the appearance of bile to the exudate.

BILE PERITONITIS WITHOUT PERFORATION

The poisonous action of bile on the various tissues of the body, as in the destruction of red blood cells, muscle, nerve, and even bacteria, has been observed in the preceding chapters. This action depends on the bile-salt concentration of the bile. Strong solutions of bile acids cause actual death and necrosis of the various tissue cells. Strong solutions dissolve bacteria.

Bile peritonitis without perforation of the bile ducts or gallbladder has been reported repeatedly. The literature has been summarized by Buchanan, 1918. The theories are: filtration; microscopic perforation; small but almost invisible perforation; a rupture, subsequently healed; and postperitoneal perforation of the common duct. No one of these theories explains all the recorded cases.

A number of cases have been reported, especially in German, French, and Italian literature, since the Buchanan review. Chemical analysis of the peritoneal fluid is lacking in all these cases. Following injection of a sublethal quantity of bile into the peritoneal cavity, there is a large effusion of

fluid. A few cubic centimeters of concentrated bile free in the peritoneal cavity cause a transudation of several hundred cubic centimeters of fluid. A very small amount of pigment colors the entire liquid content of the peritoneal cavity, thus causing a misinterpretation by many observers as to the real identity of the fluid. A quantitative chemical test for bile acids is necessary for the identification of this fluid.

BILE PERITONITIS WITH PERFORATION

CLINICAL

Cases of bile peritonitis were recorded two centuries ago. Skeete, 1785, reported the case of a boy who fell and lacerated the gallbladder. Autopsy revealed 11 liters of bile-colored fluid in the abdomen. Fryer, 1813, reported that a boy was struck in the abdomen and that 47 pints of "pure bile" were removed by four paracenteses. The boy recovered. No examination of the fluid was made. Terrier and Auvray reviewed the cases from 1750 to 1897. Paracentesis or laparotomy was done frequently. Any bile-colored fluid in the abdominal cavity was called "bile."

Some medical writers concluded that bile did little damage to the peritoneum unless there was infection: Mayos (1227), Da Costa (415), Judd and Burden (947), and Pincoffs and Boggs.

A careful review of the literature, by Gosset, Desplas, and Bonnet, revealed 111 cases with actual perforation of the gallbladder, with a mortality of 52.2 per cent. Perforation of the gallbladder into the free peritoneal cavity is more serious than perforation of a gastric or duodenal ulcer. Another series of 28 clinical cases was reported by Fifield, with 12 deaths.

Numerous references to clinical cases were given by Ehrhardt in which bile was spilled into the peritoneal cavity during operation or following trauma. If the patient died soon after the accident, the peritoneal cavity usually contained only a small quantity of fluid, indicating rapid absorption of the bile and actual cholemia with speedy death. Some

cases were reported where the operation or autopsy was done several days after the accident; the peritoneal cavity was filled with a bile-colored fluid, a protective exudate. There was a slow peritoneal absorption and a slowly developing cholemia.

The escape of bile into the abdominal cavity of man or experimental animals causes death. Of course, there is a quantitative relationship; and if only a small amount of bile or bile salts escapes, there may be few or no symptoms or signs.

There is an extensive literature on traumatic rupture of bile ducts, gallbladder, and liver. Death always results unless the extravasation of bile is stopped either by nature or by operation. Nature causes extensive adhesions to form wherever bile comes in contact with the peritoneum. If the escape of bile is slow, the adhesions wall off the bile and confine it within its normal course, or form cysts. The bile in these cysts is rapidly diluted with fluid from the serous membrane and made innocuous.

A list of several hundred reported cases of death from traumatic rupture of the gallbladder or bile ducts, postoperative rupture, and spontaneous rupture of the bile ducts with drainage of bile into the peritoneal cavity has been collected. A very high mortality rate, approximating 50 per cent, was found. Crile, in 1927, said he believed that it is quite well recognized that leakage of bile into the peritoneal cavity carries with it a great deal of risk. Perhaps this is true because the operations were performed on patients who had infected biliary passages. Infected bile has frequently been taken from the gallbladder and from the common duct. Whether or not the bile itself has destructive effects in the abdomen he was not prepared to say, but he was convinced that leakage of bile into an infected peritoneal cavity is a dangerous complication.

EXPERIMENTAL

From the experimental work on guinea-pigs and rabbits, Fraenkel and Krause attributed the ill effects of intraperitoneal injection of bile to bacteria. Guinea-pigs and rabbits

died in from 2 to 5 weeks. Very small amounts of bile, only 6 cc. for a 5-kg. dog, were used, with no effect.

Experimenting with cats and dogs, Ehrhardt sectioned the common duct and incised the gallbladder. Bile, spilled into the peritoneal cavity, was absorbed; and the thoracic duct was discolored and its fluid content yellow, even to the vein. He therefore concluded that the thoracic duct is essential to cholemia. He stated that bile peritonitis causes death with the picture of icterus gravis.

The common duct was sectioned in 7 rabbits by Ruffer and Crenderopoulo. All the rabbits died of peritonitis within 4 days. The gallbladder was then incised in 2 rabbits, but they lived. Autopsy showed a marked plastic exudate about the gallbladder, closing the incision. There was a chemotactic effect by the bile, producing a migration of leukocytes and the formation of a membrane, with incapsulation of bile in small pockets in some instances. There was a fall of temperature, a diminution of blood pressure, a decreased red-blood-cell count, a leukocytosis with diminution of eosinophiles, and an increase of lymphocytes.

Intraperitoneal injection of 15 cc. of bile in rabbits weighing 1,000 gm. caused death within a few hours (Sellards [1742]). Beef bile and sodium glycocholate in concentrations of 5-13 per cent, injected intravenously into guinea-pigs and rabbits, caused death within 8-15 hours. At autopsy some free fluid was found in the peritoneal cavity. Loci of hemorrhages in the lungs, intestine, and stomach were verified by histologic examination. Guinea-pigs weighing 250-75 gm. were also injected intraperitoneally with a 5 per cent solution of sodium glycocholate, 0.1 gm., in physiologic sodium chloride. From 1-2 hours following the injection hiccuping was observed, the respiratory rate was increased, and the animals became comatose; death resulted in 8-15 hours. With large doses of bile salt, death occurred in 1-2 hours. When smaller amounts were injected, death was deferred for a few days or longer. If the amount were small enough, the animal recovered.

Intraperitoneal injection of 0.25-0.5 cc. of bile per kilo-

gram killed rabbits weighing about 2,200 gm. within 24 hours. Bunting and Brown stated that bile produces necrosis of every type of tissue with which it comes in contact. Autopsy revealed extensive edema of the lungs and a considerable amount of bile-stained serous exudate in the peritoneal cavity.

In work with dogs, Wangenstein (2049) found that the bile salts in bile caused death. The early death was due to the large taurocholic content of dog bile, which is more toxic than the glycocholic acid content of bile in the herbivores.

Horrall (854) said in 1929: "The questions that naturally arise are in regard to the effect of autogenous bile free in the peritoneal cavity; whether bacteria are the sole harmful agents or whether they do not have any relation to the symptoms and the condition found at autopsy in bile peritonitis; what will be the effect of bile continuously pouring out into the peritoneal cavity; what difference in symptoms will be produced by varying the quantity of bile and what effect will bile from other dogs injected into the peritoneal cavity produce.

METHODS

"1. All experiments were performed on dogs anesthetized with ether and operated on aseptically. The abdomen was opened along the edge of the right rectus muscle, the tip of the gallbladder caught up with forceps, a purse-string suture placed about the tip, and then the gallbladder opened, letting the bile spill out into the peritoneal cavity; the opening was then closed with the purse-string suture, the edges of the bladder being inverted. The intestines were moved about to insure thorough distribution of the bile over the peritoneum, and the abdomen was closed. General symptoms were noted, and various tests applied as indicated.

"2. An intraperitoneal fistula of the gallbladder was made aseptically under ether anesthesia. The bile was spilled into the peritoneal cavity and stirred about so that it would come into contact with much of the peritoneum. The edges of the

opening in the gallbladder were stitched back, to prevent spontaneous closure, and the abdomen closed.

"3. Bile was removed aseptically from the gallbladders of living dogs under anesthesia with a syringe and needle. Bile was collected from eight to twelve dogs, mixed, culture taken and immediately injected by paracentesis into the peritoneal cavity of dogs, the quantity for single dosage being varied, and repeated small doses also being given to other dogs. Part of the bile was sterilized in an autoclave at 15 pounds pressure for thirty minutes before injection.

I. THE EFFECT OF BILE FROM THE GALLBLADDER SPILLED INTO THE
PERITONEAL CAVITY

"The animal was operated on February 17. There was slight postoperative vomiting; the animal was fed the second day; food and water were both retained; the animal was rather thirsty; it was up and walking about and ill effects were not apparent; the urine showed a slight trace of bile, and no albumin or sugar; the actions were entirely normal. On May 5, the dog was killed so the pathologic effects of the bile could be noted. At autopsy, the dog was well nourished and in excellent condition. An entirely normal condition was found except there were a few adhesions about the tip of the gallbladder where the incision had been made. Cultures were made from the bile at the time of operation and from the peritoneal cavity at autopsy. At operation, staphylococci were found in one case and a bacillus in another. Bacteria were not found at autopsy in any case.

2. THE EFFECT OF BILE CONTINUOUSLY POURING OUT INTO THE
PERITONEAL CAVITY

"Dog 6.—The animal weighed 10 Kg., a fistula of the gallbladder was made. The animal vomited frequently; severe retching occurred; thirty minutes later there was a bowel movement. Later, frequent watery stools were passed; seven hours later, the animal staggered and was much weaker and rather listless; fifteen hours later, the heart was irregular and slow and the respirations slow and sluggish. The dog was

hardly able to stand, and gradually became weaker and passed into coma, it did not have convulsions, was difficult to arouse, and passed frequent bloody stools. Twenty-two hours later, it died in coma; no urine was passed. At autopsy, the lungs were slightly congested in spots; the heart was soft and flabby; the peritoneal cavity contained 275 cc. of slightly bloody fluid deeply stained with bile and a few gelatinous masses. The peritoneum was stained yellow, but this was most marked in the diaphragmatic portion; the peritoneum of the lesser omental cavity was also stained; the liver was markedly congested; bile was not found in the ducts or bladder; the lumen of the gallbladder was open. The intestines were covered with many small petechiae, which were most plentiful over the ileum; the intestine did not contain bile; the mucosa of the colon and small intestine was markedly congested, and the contents of the colon watery and bloody; the greater omentum was stained deep yellow and contained numerous petechiae. The kidneys were congested and bluish-red; the urinary bladder contained 2 cc. of heavy bile colored urine; the chemical tests showed much bile and 5 per cent of albumin. Microscopic examination showed many red blood cells, few white blood cells, also renal cells and debris; cultures were negative.

3. THE EFFECT OF INTRAPERITONEAL INJECTION OF BILE

"Dog 13.—Into an animal weighing 4.2 Kg., 25.2 cc. of bile from the gallbladder were injected intraperitoneally, 6 cc. per kilogram of body weight. The symptoms were similar to those in the foregoing cases but progressed more rapidly; death occurred in fifteen hours. The conditions found at autopsy were similar, except that there was more clotted blood in the peritoneal cavity. Cultures were negative.

4. EFFECT OF SUBLETHAL DOSE GIVEN INTRAPERITONEALLY

"Dog 23.—Into an animal weighing 4.2 Kg., 16.8 cc. of bile from gallbladder were injected intraperitoneally, 4 cc. per kilogram of body weight. There was immediate spasticity

of the abdominal muscles, and the dog appeared to be in distress. (Intraperitoneal injections of physiologic sodium chloride solutions did not cause rigidity and only slight pain when paracentesis was performed.) Five minutes later, defecation and retching occurred. Ten minutes later, vomiting and staggering were noticed; the retching and vomiting were repeated every few minutes. This was accompanied by thirst and lapping of water and frequent stools, which became watery and then bloody. Nine hours later, there was marked edema of the eyelids and lips; a small amount of urine was passed, which contained bile and a trace of albumin; the heart was slow and irregular; respirations were slow. Eighteen hours later, the condition had returned practically to normal except for anuria. Thirty hours later, the urine showed bile and much albumin; some edema of the eyelids occurred. On the seventh day, the condition was good except for a slight fluctuating edema of the eyelids; the urine showed bile and albumin. On the twenty-eighth day, edema of the eyelids persisted; the urine showed albumin in varying amounts. On the thirty-first day the animal died. Autopsy showed many patches of bronchopneumonia in the lungs; the heart was flabby; 50 cc. of bile-colored peritoneal fluid were obtained; the liver showed a nutmeg appearance; the kidneys were congested; the suprarenals were diminished, especially in the medulla.

5. INFLUENCE OF BACTERIA

"In a few instances, bacterial growths were obtained from the bile of other dogs and used for these injections. Bacteria were also obtained from the peritoneal fluid following death of the dog into which bile had been injected; the cultures contained staphylococci or colon bacilli. The bacteria in most instances certainly could not cause the symptoms and death as the same reactions were obtained in dogs in which bacteria were not found in the bile used or in the peritoneal fluid at postmortem. Nevertheless, for evidence on this point, the following experiment was done:

"Dog 30.—Into an animal weighing 1.6 Kg., 8 cc. of sterilized bile were injected intraperitoneally, 5 cc. per kilogram of body weight. Death occurred in twenty-four hours. The symptoms and the condition found at autopsy were the ones usually seen. Cultures were negative.

SUMMARY

"Bile from the gallbladder was spilled into the peritoneal cavity in twenty-five dogs. There were no deaths, and the effects were slight and transitory. Some of the dogs vomited, a few had diarrhea, and the urine contained varying amounts of bile pigment. The amount of jaundice present was just perceptible. Bacteria were not the cause of these symptoms, as sterile or infected bile gave the same results.

"Intraperitoneal fistula of the gallbladder in seven dogs permitted sufficient bile to pass into the peritoneal cavity to cause death within twenty-four hours. If the fistula was partly closed, the dog lived longer, and if it was completely closed, the effects were transitory. The symptoms preceding death were: bradycardia, low blood pressure, slow respiration, anuria and coma, and in many cases edema.

"Intraperitoneal injection of bile from the gallbladder of dogs into nine dogs in amounts of 5 cc. or more per kilogram of body weight caused death within twenty-four hours.

CLINICAL SYMPTOMS AND SIGNS OF BILE PERITONITIS IN DOGS

"Rigidity of the abdominal muscles, especially in the right upper quadrant, and retching and vomiting occur; pain may be extremely severe; early defecation and later, watery or bloody stools occur; bradycardia, irregular heart, weak pulse, slow and irregular respiration, early restlessness, later, lethargy, and finally coma and death occur; urine, if obtainable, contains bile and albumin (usually total anuria); edema was present in 30 per cent of the dogs; jaundice was slight and sometimes questionable. Apparently the renal portal in dogs is low for bile pigments, as they are rapidly excreted in the urine."

DISCUSSION

If a small amount of bile escapes into the peritoneal cavity and is rapidly scattered over the peritoneal membrane, there is immediately a great outpouring of fluid from the serous membrane. Frequently 12 hours following the injection of 20-40 cc. of gallbladder bile into the peritoneal cavity of a dog weighing 12 kg., 500 cc. of fluid can be removed.

Probably the most serious misinterpretation of the effects of bile occurs in calling this 500 cc. of fluid "bile." The writer has been told frequently by reputable surgeons that several hours or days following trauma they have opened the abdomen of patients and removed several quarts of "bile." Of course, the fluid contained bile pigment and it was, therefore, called "bile." Bile was present, but the bile had been greatly diluted by the secretion of fluid from the peritoneum, owing to the chemical stimulation of the bile salts. If the normal bile contains from 1 to 15 per cent bile acids and the dilution is in proportion to that found experimentally, the fluid found by the surgeons in the peritoneal cavity would have contained only one-twenty-fifth as much bile salts as the whole bile itself.

A case with "500-600 cc. bile" about the liver following operation was reported by Walters and Bollman (2042) in 1928. Thomas Skeete (292, cited), as early as 1785, pointed out the fallacy of calling a fluid "bile" just because of its color.

In order to determine how much bile is present in the peritoneal fluid and, thereby, its toxicity, it is necessary to make a quantitative chemical analysis of the fluid. Visual analysis of the bilirubin content is not sufficient, as many complicating factors, such as extravasation of blood, are involved.

All evidence, experimental and clinical, tends to prove that bile does cause a peritonitis. This peritonitis is chemical and, if extensive enough, causes death in all animals. Numerous comparisons have been made with different kinds of animals, all to the same end.

The various biles in the same peritoneal cavity have numerous degrees of toxicity, and the same bile in different peritoneal cavities has many degrees of toxicity. Bile of the different animals contains diverse bile salts of varying degrees of toxicity and concentrations. These variations are given in the chapter, "Toxicity of Bile Acids."

The comparison of dog bile with human bile has led many to doubt the toxicity of human bile. It must not be forgotten that bile in the peritoneal cavity acts quantitatively. It takes more bile to kill a large dog than a small dog. Then one must conclude that it takes still more bile to kill an adult human being. The concentration of the two biles is markedly different, the human bile being much more dilute. Also, the dog bile contains chiefly sodium taurocholate, while the human bile contains mainly sodium glycocholate. The protective substances, such as cholesterol, lecithin, and mucin, are present in much larger quantities in human bile than in dog bile. Thus, in order to compare the toxicity of various biles, the numerous variations in the different biles must be kept in mind.

Recent work has demonstrated the presence of bacteria in the exudate following injection of bile into the dog, intraperitoneally, subcutaneously, and intrathoracically. The cultures of the various tissues of the dog untreated with bile showed similar growths of bacteria. It is generally conceded now that bacteria may be found in the tissues of the body which were previously supposed to be sterile. Metastatic abscesses are definite evidence that bacteria are transported to many parts of the body. Tissue culture has not been done extensively enough to make definite statements in regard to man, though *B. welchii* has been found in several tissues in the dog.

Weinberg and Levenson found a large variety of bacteria in the peritoneal cavity of guinea-pigs following intraperitoneal injection of sterile bile. Of 76 guinea-pigs injected, 33 had sterile and 43 had infected peritoneal exudates. The bacteria

found were: *B. coli*, in 14 animals; staphylococci, 9; enterococci, 8; *B. perfringens*, 6; streptococci, 6; *B. paratyphosus*, 2; anaerobes, 3; aerobes, 6. They concluded that bile aids the passage of bacteria from the intestine into the peritoneal cavity.

Bacillus welchii has been demonstrated in the peritoneal fluid following intraperitoneal injection of bile, and death of the animal was attributed to *B. welchii* rather than to the bile (Rewbridge [1957]).

The intraperitoneal injection of bile causes death in a large variety of laboratory animals. The escape of bile into the peritoneum of man, particularly in untreated traumatic lesions of the bile ducts, is followed by death in a large percentage of cases. In man, since *B. welchii* occurred but rarely either in the bile or in the liver, the danger from gas bacilli is negligible, according to the recent work of Judd.

Bacteria are notoriously toxic under certain conditions, and their mere presence is not indicative of their destructive ability. *Bacillus welchii* is a common inhabitant of the intestinal tract of many animals, but only under certain conditions does it become deadly. The effect of bile on the growth of *B. welchii* has not yet been determined. From recent work it might seem that bile has a chemotactic action on *B. welchii* or stimulates its growth. It is necessary for more work to be done in vivo and in vitro to determine the action of bile on the growth of *B. welchii* and, also, on the formation of its specific toxin.

An anaerobic bacillus resembling *B. welchii* has been isolated from the bacterial flora of the liver and muscle of normal dogs by Trusler and Reeves. This bacillus does not produce endotoxins and, when cultured in the abdomen, does not cause death, but does cause death when cultured with liver. Further investigations proved that the bile salts do not cause *Clostridium welchii* to invade the peritoneal cavity. This bacillus should not be confused with the very virulent *B. aërogenes capsulatus*.

Adhesions following extravasation of bile into the abdominal cavity are frequently observed. These adhesions are at first extensive but are pliant and friable. A few weeks following the contact of the peritoneum with bile these adhesions gradually begin to disappear, and there remain only the strong bands or strands. Experimentally, these adhesions may be produced in the peritoneal or thoracic cavities. They are localized in the quadrant into which the bile has been injected unless too large an amount has been given, causing the chemical irritant to spread.

The larger bands of adhesions may cause serious symptoms later, mechanically inducing acute obstruction of the intestine. All bile getting into the peritoneal cavity during operation should be carefully removed, and the site of contact should be sponged with physiologic salt solution to dilute any remaining irritant of the serous membrane. A mild bile peritonitis with slow chemical absorption may cause a fibrinous exudate sometimes found at operation. The channels of absorption of toxic and nontoxic substances from the peritoneal cavity have been studied by a number of investigators. Work done by McGuire tended to show that the path of absorption in peritonitis is not by way of the lymph vessels and the thoracic duct. The intraperitoneal accumulation of fluid in bile peritonitis, according to Moon and Morgan and to Andrews, Harkins, and Harmon, causes secondary surgical shock. There is a decrease in the volume of the circulating fluid equal to 3 per cent of the body weight. The peritoneal fluid is similar to the blood serum. The blood pressure decreases, and the hemoglobin increases. When subcutaneous injection is used, there is a shift of fluid to the injected side. The extravasation of fluid following injection of bile salts produces shock, according to definition.

This marked accumulation of fluid was referred to by Horrall as "dehydration." A rather interesting observation was made by the last-named investigator. He showed that

the smaller the amount of fluid that accumulates in bile peritonitis, the sooner death occurs. The changes which occur are: a fall of blood pressure, an increase in rate of respiration and heartbeat, blood in the urine, petechial hemorrhages in the myocardium, lungs, brain, and intestine, and subserosa in the peritoneal, pleural, and joint cavities. Certainly the toxic bile in the blood stream causes the rupture of capillaries at points distant from the site of injection. The intravenous injection in dogs of filtered peritoneal fluid removed from moribund dogs with bile peritonitis does not cause a marked fall in blood pressure or severe toxic symptoms. The peritoneal exudate does not contain the original total toxicity. A part of the bile salts has been absorbed and a part probably has been detoxified by combining with the protein in the exudate and by the phagocytes which have a definite affinity for the bile acids. It is well known that the intravenous injection of bile salts in serum is much less toxic than bile salts in physiologic salt solution.

TREATMENT

From recent experimental work Horrall (854) has shown that neither calcium chloride nor calcium lactate detoxifies bile and that the end is only hastened by their use intraperitoneally. As yet there is no chemical antidote, although cholesterol and lecithin do slightly inhibit the toxicity. The treatment that has been most satisfactory necessitates early recognition of bile peritonitis and open operation with closure of the bile leaks, thorough lavage of the peritoneal cavity with physiologic sodium chloride solution, leaving a fair quantity in the peritoneal cavity, followed by closure. Fluids, intravenous and subcutaneous, to wash out and dilute the absorbed toxic substances produce a more favorable course. Bile causes a marked dehydration; so restoration of fluids is necessary.

RÉSUMÉ

Bile peritonitis is caused by the toxic action of bile acids.

Bile acids exert a toxic effect on the heart, kidneys, blood, and blood capillaries and on all tissue with which they come in contact.

Bacteria has little or no effect if the peritonitis is fatal within a few hours.

Secondary surgical shock is a very important result of the toxic action of bile acids.

It has been well established that bile, injected subcutaneously, causes tissue necrosis, and even a large aseptic abscess.

Why, then, can it not cause bile peritonitis?

CHAPTER XXII

BILE RETENTION: ICTERUS

ICTERUS is one of the oldest known "diseases." It was very common in early Greece, according to history, and is referred to in the literature through all the ages. The layman very frequently observes severe cases of yellow pigmentation of the skin and eyes. The tint of the skin may vary from a bright lemon to orange, olive, or even a dark green. It is probably more common in the tropical regions, and especially in regions where malaria is prevalent.

The words for icterus in the various languages are significant: in English, *jaundice*, meaning yellow skin; in French, *jaune*, for yellow; in Latin, *morbus regius*, for kingly disease; and in German, *Gelbsucht*, meaning yellow sickness.

Yellow staining of the skin has been frequently feigned by soldiers and sailors. The skin is colored yellow with saffron, tumeric, and such; but the conjunctivae are not colored, and soap and water or chloride of lime will remove the coloring. If rhubarb or santonin are taken, the urine will be colored, but it does not react with nitric acid. Carbazotate or potassium picrate, taken internally, will stain the skin and the urine; but the urine does not give the test for bile pigment (1082, p. 375).

Jaundice may be physiologic. In the horse the blood serum has a very distinct orange appearance, indicating the presence of pigments in a high degree. In the cows of Guernsey the fat is a natural orange color (Budd). In man the normal blood serum has different degrees of pigmentation, from almost clear colorless to a lemon yellow. The pigment may be more concentrated—almost an orange—and the serum be within normal limits. Some races have more bile pigment in the blood than others. This is particularly noticeable in

Negroes of the west coast of Africa, who are not jaundiced (Budd). Normal human serum contains 1:1,000,000–1:400,000 bilirubin; a healthy man with sallow skin may show 1:80,000, a physiologic hyperbilirubinemia. This pigmentation varies considerably in different individuals and at different times of the day, according to the amount of exercise. It may also be influenced by the type of food intake.

Local icterus appears following extravasations of blood in the tissues. Rhombic plate crystals were first observed by Virchow in an old hematoma. Hematoidin seems to be chemically identical with bilirubin found in old hemorrhagic areas (Whipple). The successive changes in color of the black-and-blue area in the skin, depending on time, are due to the oxidation changes of the blood pigment, probably bilirubin oxidation and reduction.

Generalized icterus appears when there is an excess of bile pigment in the blood stream. This may be due to the failure of the liver to eliminate the pigment normally produced, or it may be due to the rapid overproduction of pigment, as in hemolytic icterus.

The term *jaundice* usually means that there is yellow skin and sclerae and an increase of the bilirubin in the blood stream. When the pigment in the blood increases sufficiently, it then passes over into the urine.

ETIOLOGY

There has been considerable confusion as to whether the actual toxic symptoms in jaundice are due directly to the bile or to some one substance in the bile; or whether they are due to absorption of toxic substances from necrotic areas which the bile has produced, such as protein split-products. In obstructive jaundice, are the liver changes due to bile itself, or are the general symptoms produced by necrotic products of the liver? Does bile cause a series of symptoms which end fatally, or does the terminal infection take over these symptoms which were originally started by the bile? In man, does

bile itself produce the intoxication? Permanent damage may be due to small amounts of bile, acting repeatedly; but when once a trend of symptoms is initiated, may not the toxic cause be removed and still the course progress? These are controversial questions which future research may answer.

CLASSIFICATION OF JAUNDICE

Clinical observation usually discloses first the yellow discoloration of the sclerae; this is followed by a gradually increasing yellow color of the skin. The bile pigment remains in solution in alkaline media when associated with bile salts. There seems to be only a slight pigmentation of the muscle cells. Quincke found the intercellular fibrils of connective tissue cells pigmented with longer retention of the bilirubin. After death practically all the tissues are pigmented.

Bile pigment may be present in such small amounts that the tissue is slightly stained, or it may accumulate until granules are deposited. Crystals of bilirubin have been frequently seen in body fluids and tissues in jaundice. It has been suggested that there is a difference in the selective activity or affinity of the various body cells for bilirubin. Normally the liver cells remove it from the blood before the concentration in the blood reaches 1 part in 50,000 (van den Bergh). When the concentration in the blood exceeds this proportion, the tissues begin to take up the pigment or the blood fails to remove it from them.

The question as to a definite renal threshold for bilirubin does not seem to be supported by adequate data. It was thought that bilirubin was absent from the urine if the blood bilirubin was below 4 units. Bilirubin has been found in the urine with the blood concentration as low as 0.12 mg. per 100 cc. If there is a renal threshold, it must be very much lower than that previously supposed (Rabinowich). Kidney diseases may affect the bilirubin output in the urine.

Van den Bergh and Snapper (1973), in 1914, found that bilirubin passes into the urine when the concentration in the

blood serum is from 1:50,000 to 1:60,000. In some cases where there is bilirubinemia there is no bilirubinuria. If the kidney threshold for bilirubin is low, as in the dog, the yellowish coloring of the body tissues is slow to develop or will develop only to a slight degree. In dissociated biliary retention, according to Lemierre, Brulé, and Garban, there may be an excretion of pigment in the bile without bile salts, or the pigment may be retained in the bile and the salts excreted.

The length of time necessary for the development of jaundice following obstruction of the common duct in dogs is from 36 to 48 hours.

The classification of icterus by Quincke and Hoppe-Seyler (1857) was based on pathologic findings and etiology. Van Bergmann (2004) classified icterus as follows: mechanical stasis icterus, obstruction of the larger bile ducts or bile capillaries; icterus without obstruction of the larger bile passages; damage to the liver cells, acute yellow atrophy, infectious icterus, syphilitic icterus, pernicious-anemia icterus, and icterus neonatorum.

Gilbert's classification, based on analyses of blood and urine, was: choloric icterus and acholoric icterus.

Lemierre and Brulé classified icterus as follows: *cholories pigmentaires*, *cholories salines*, *cholories dissociées*, *cholorie totale*, and *ictère total*—retention of pigment salts and cholesterol.

It is generally thought that jaundice is primarily obstructive, that is, there is obstruction of the extrahepatic bile ducts, obstruction of the intrahepatic bile ducts, and obstruction of the hepatic cells themselves, as occurs in the chemical poisoning of the liver.

Chabrol (337) classified icterus as follows: icterus by retention, (a) complete retention and (b) incomplete retention; and icterus by polycholia and by hemolysis (mixed icterus). The clinical classifications were listed as icterus neonatorum, simple acholoric icterus, *ictère émotif*, icterus of pregnancy, icterus from poisons, syphilitic icterus, infection icterus, ca-

tarrhal icterus, icterus from gallstones, icterus with chronic pancreatitis, icterus from chronic obstruction of common duct, cirrhotic icterus, and icterus gravis. This classification included a large number of types of icterus; for example, under icterus of the new-born was included jaundice caused by congenital malformations of bile passages and syphilis. Under acholuric icterus was included familial icterus, splenomegaly with icterus, and pernicious-anemia icterus.

The mechanism of the production of icterus in man, according to the classification of McNee, with percentages given by Hartman, are: obstructive, 70 per cent, with occlusion or obstruction of extrahepatic bile passages; carcinoma, 25 per cent; stones, 20 per cent, and stricture of the common duct, 10 per cent; intrahepatic, 23 per cent, with obstruction of parenchyma or finer bile passages; hemolytic, 7 per cent, with increased destruction of red blood cells and involvement of bone marrow and spleen.

Attempts have been made to differentiate the causes of jaundice by the van den Bergh reaction (McNee). In obstructive jaundice, bilirubin gives a direct reaction (van den Bergh); while in hemolytic jaundice, there is an indirect reaction.

In the experimental work of Davies and Dodds it was found that the van den Bergh test for bilirubin depended on the pH of the solution or on oxidative changes occurring in the pigment. Biliverdin gave only the indirect reaction, and clinical and experimental evidence was offered to show that bilirubin can be oxidized to biliverdin in the circulation. If the bilirubin was confined where oxidation could not take place, then the test was for bilirubin and was direct; but if there was only a small amount of bilirubin, as in early and late jaundice, then there was an opportunity for bilirubin to become oxidized into biliverdin, and the reaction became indirect.

According to Lepehne, the direct, prompt van den Bergh reaction is found in the serum of patients with mechanical stasis, treated and untreated syphilis, acute yellow atrophy

of the liver, phosphorus and chloroform poisoning, cholangitis, septic hemolysis, and gallstones. The direct delayed reaction is found in patients with hemolytic disease, icterus neonatorum, light stasis, and receding jaundice in the foregoing patients who originally gave a direct, prompt reaction. The direct diphasic reaction is found in convalescent patients who gave a direct, prompt reaction and also in patients with mild forms of the same.

The classification of McVicar and Fitts depended on the reaction of jaundiced serum to the van den Bergh test, either direct or indirect; height and behavior of serum pigment curve, as determined by the van den Bergh reaction or icterus index; the quantity of bile reaching the intestine, as determined by the duodenal tube; and the presence or absence of pain, and its character. Aschoff (81) and McNee (1249) in recent reviews base their differential diagnoses of jaundice on nontoxic bilirubin. These classifications used the qualitative and quantitative variations in the van den Bergh reactions. No mention was made of the toxic cholic-acid constituent of bile.

The amount of disability due to the presence of bile alone in the system is difficult to determine. The infection or other etiologic factor causing the retention of bile with jaundice complicates the interpretation. Also, the liver functions are impaired. There is an increase in the toxic nitrogenous substances in the blood (Bickel, 175), owing to the failure of the liver to detoxify and to the inability of the kidney to excrete normally.

Fasting or starvation icterus is the only functional type now considered. Evidence is inadequate for "emotional icterus."

SYMPTOMS OF JAUNDICE

All the pathologic conditions which accompany jaundice have been attributed to bile. From the time of Saunders and of Leyden, studies of the liver have been made following ligation of the common duct. Feltz and Ritter concluded that

ligation of the common duct in animals causes symptoms similar to those in obstruction of the bile ducts in man. Snell has shown, by a modification of the Pettenkofer reaction, that, following biliary obstruction, the bile acids increase rapidly in the blood, reach a maximum in 2 or 3 weeks, and decline to normal in 50 days, if the gallbladder is intact. There is some slight fluctuation afterward. With the diminution of bile acids in the blood, however, there is no abatement of the clinical symptoms. Rous and McMaster (1639), Katayama and Shattuck, Katayama, and Killian concluded that the secretion of bile is never inhibited, only diverted.

It would be interesting to find out just what becomes of the bile acids in long-continued obstructive jaundice. They are not eliminated as such entirely in the urine. There is a possibility that the manufacture of bile acids is diminished, parallel with the diminution in general metabolism. When jaundice has not continued too long, relief of the obstruction is followed by a prompt return to normal.

Andrews, Thomas, and Schlegel (58) had definite ideas in regard to what causes the toxic symptoms of icterus, namely, bile salts, bile pigments, glycogen starvation, polypeptides, and amino acids. Therefore, they arrived at the conclusion that the toxin must arise in the liver, since hepatectomy prevents the symptoms. Andrews and his collaborators concluded that the toxic symptoms are explained by a leakage of protein from the liver, caused by a disturbance in the mineral-salt balance.

This is a field for much-needed investigation. At the present time, one cannot advise rational therapy in cholemic conditions (Bayer [127]).

In just what way bile is toxic in obstructive jaundice is difficult to say. Nevertheless, there appears to the clinician a series of symptoms fairly characteristic, and to the surgeon a warning to institute preoperative treatment.

According to recent work, the bile salts in the blood stream are at first increased and later decreased, coming to nearly

normal. Blood pressure, according to some writers, at first is slightly increased; but all agree that later in jaundice the blood pressure is decreased. There are so many causes for decreased blood pressure that this cannot be attributed entirely to bile itself. Electrocardiographic tracings do not show constant findings, and there is no unquestioned experimental evidence to justify basing the series of symptoms observed in jaundice on the presence of bile or any of its constituents in the blood stream or other body tissues. In fact, after jaundice has continued a considerable length of time, there is an actual diminution of bile production.

In most cases the mention of jaundice brings to mind the picture of some sort of obstruction to the biliary passages. The interference with the outflow of the bile may be assumed to be located in either the larger ducts or the minutest canaliculi; but in any event, it represents a mechanical interference with the discharge of the accumulating secretion. There are, admittedly, instances of jaundice of nonobstructive origin that have been described as congenital hemolytic icterus. The conception of such instances of pigment formation without participation of the liver has become plainer recently, since the extrahepatic origin of bilirubin has been demonstrated. Drury and Rous have demonstrated a type of functional, rather than mechanical, suppression of biliary pigment excretion that arises in certain types of severe hepatic intoxication, notably after poisoning with chloroform. The functional inability of the liver cells to remove and excrete bilirubin from the blood in such circumstances is indicated by the production of a colorless, watery bile (Drury). Jaundice may occur without any hepatic lesion, owing to failure of the liver to eliminate pigment (Garnier).

Jaundice may cause abnormal substances to be liberated following destruction of liver cells, according to Bowler; but Morawitz and Bierich did not find sufficient evidence for this conclusion. The intoxication of jaundice may be due to poisons other than bile, according to Rolleston and McNee. The

liver may fail to stop poisons coming from the intestine. Putrefaction products may increase because of absence of bile from the intestine; a reduction of blood alkalinity may cause toxic symptoms. In ordinary intoxication of jaundice, Bowler placed bile salts at the head of the list of possible toxic substances.

Cholemic nervous symptoms, such as twitching, ataxia, somnolence, and coma, are frequently found in severe intoxications; but bile salts have not been definitely proved to be the cause. There are functional changes in the hepatic cells; variations in the method of handling glycogen; alteration in fibrinogen; and markedly altered nitrogen metabolism, disturbing the acid-base equilibrium; and in addition the liver may be unable to remove or detoxify poisonous substances. Gilbert, Chabrol, and Bénard showed by new tests that there is an increase of bile salts in the blood in icterus, especially in early cases. Aldrich and Bledsoe found an increase in bile acids in various forms of jaundice. Windaus (2128) reported that bilirubin and bile acids increase in the blood in the first three weeks of liver-function disturbance. Blankenhorn (192) described many cases of cholemia, and a few with choluria, which indicated a retention of bile acids in the blood or in the body tissues associated with a kidney irritation.

Bile acids were found by Minkowski and Naunyn in the blood and tissues after partial extirpation of the liver. Following total extirpation, no acids were found.

Is partial extirpation of the liver comparable to obstructive jaundice?

The symptoms of icterus are due to the toxicity of bile, with decrease in pulse rate, hemorrhages, loss of weight, and albuminuria, according to Voy (426, cited). All of these symptoms are due to the action of bile on the living tissues. The unfavorable syndrome of cholemia is associated with the presence of bile in the blood and in increasingly developing jaundice. Early in the disease there is a slow heart, twitching, and restlessness; later, somnolence and coma. Windle

noted that in most cases of obstructive jaundice the heart rate is normal, but that in catarrhal jaundice there is bradycardia. McVicar and Fitts said that the slow heart in jaundice has proved almost a myth.

The absolute concentration of bile acids in the blood or other body tissues is still unknown. The bilirubin content of the blood serum does not run parallel with the bile-acid content, according to the work of Hoover and Blankenhorn. These substances are not always excreted in parallel quantities in the urine—a renal dissociation. From most recent experimental work it would seem that the appearance of bile acids in the blood is only transitory, but they are not eliminated quantitatively in the urine and they do not go into the enterohepatic circulation; so the question as to the fate of bile in jaundice is important. Bile acids are gradually decreased but continue in a small quantity. The bile pigments increase early but fall to a lower level, which remains constant. Injection of taurocholic acid causes elimination of that acid in the urine as such, but in jaundice the urine nitrogen is increased and approaches a constant. The neutral sulphur is also increased and approaches a constant. This may account for taurocholic-acid elimination but does not explain the disappearance of the glycocholic acid, which is predominant in the herbivores. In certain stages of infectious jaundice, Lemierre, Brulé, Weill, and Lordat found a retention of bile pigments with excretion of bile salts into the intestine, and at times the reverse, as shown by the absence of alimentary lipemia. Widal and the French school observed a dissociated jaundice. In catarrhal jaundice the hepatic cells are damaged, and in turn the finer biliary capillaries are obstructed. The reverse may be true; it is difficult to determine which is the first to occur. In jaundice from infection and jaundice due to certain poisons, Eppinger (534) found that the finer capillaries of the liver are often blocked by small casts or thrombi, and that behind these tiny obstructions there are dilations of the bile capillaries. Elliott and Walshe observed

that the toxic state of severe hepatic insufficiency, sometimes spoken of as "cholemia," is associated with plantar extensor response and is not concerned with bile pigments. It also is not related to suppression of urea formation or sugar output from glycogen, as in acidosis or uremia; an acute cholemia gave the prognosis of death within a few days, when associated with the extensor form of the plantar, or Babinsky, response. The supposition is that, in addition to the liver destruction, there is also damage to the tissue of the central nervous system from the cholemia.

The blood urea in jaundice is high. This may be attributed to failure of renal function and to increased hepatic function. As soon as the renal function improves and hepatic function lowers, the blood urea diminishes to normal. An increase of lactic acid in the blood is associated with a disturbance of the hepatic parenchymal cells (Mizuno). Brakefield and Schmidt have observed a greatly diminished ability of jaundiced dogs and rabbits to detoxify benzoic acid. It would appear from this that the animal body in jaundice is not able to take care of certain poisons, as it normally does. Bisso (185) said: "The liver is the mightiest protective organ in the body," because it eliminates toxins in the bile.

In clinical jaundice, Bouchard (230) found that a time interval is necessary for the tissues to absorb the pigment. Either the poisoning or some of the symptoms may occur several days before visible evidence of discoloration of the body tissues. Stadelmann (1824) found in icterus a slow pulse, weak heart, bleeding of the skin and various organs, a sluggish brain, and delirium. The causes may be: cholesterol (he questions this being the poisonous substance); the bile pigments, particularly bilirubin (which he also questions); and then the bile acids. Jaccoud found the pulse to be 20-30 under normal when there is no fever, and fever rarely accompanies this condition unless there is some complication.

Symptoms of jaundice were classified as follows by Mann and Bollman (1189): bile pigment in the urine, plasma, and

sclerotic and mucous membranes. If the gallbladder has been removed, bile pigment in the urine and plasma appear within 3-6 hours; if not, the pigment appears in the urine much later. The sclerotic and mucous membranes become yellow within 24 hours.

The symptoms of icterus were classified by Quinke and Hoppe-Seyler (1527) as: yellow coloring of the skin, conjunctiva, and sclerae; coloring of the urine, sweat, exudates, milk, and blood serum; enlargement of the spleen and liver; gastrointestinal disturbances with no absorption of fats and with colorless stool; heart action slowed; temperature below normal. They (1527) also classified pain according to its variations; feces as to color, odor, and frequency; urine as to color and amount; hemorrhage of skin, mucosa, and retina; pruritus; heart as to rate; mental symptoms as to delirium and coma; eyes as to xanthopsia and hemorrhage; variation in weight; and variation in the coagulation time of the blood.

The following symptoms were listed by Frerichs (634, 1: 93): conjunctiva becomes yellow; yellow skin; urine pigmented, blood serum pigmented; sweat may be pigmented; saliva may be pigmented; there may be itchiness of the skin; derangement of general sensations; great exhaustion and debility, sadness, peevishness of temper, headache, giddiness; taste and sight change; bradycardia; temperature unchanged; and derangement of digestion.

Urinary nitrogen following ligation of the common duct increases and remains high, according to Brakefield and Schmidt. Injection of bile acids (taurocholic) causes a rise in nitrogen excretion. Probably as a result of the toxemia of jaundice, a breakdown of the tissue proteins (von Norden) occurs, which causes an increase in urinary nitrogen and neutral sulphur. Bile pigment has a maximum output in the urine soon after the onset of jaundice.

Horral and Carlson recorded the manifestations of toxicity produced by bile as: heart rate decreased and irregular; blood pressure decreased; vomiting, bloody diarrhea; anuria,

or if there is urine it contains albumin, hemoglobin, red blood cells, and—later—casts, cellular then hyaline; the respiration amplitude is decreased, the rate increased, edema of the lungs, and frequently pneumonia; in the central nervous system, convulsions (tonic, clonic, or intermittent) and—later—coma; local bile peritonitis (bile in peritoneum); and local abscess from subcutaneous injection.

POLYCHOLIA (SUPERABUNDANCE OF BILE)

Experimental evidence has shown that bile temporarily can be increased quantitatively and qualitatively by certain diets, and especially by the feeding of bile salts. The ordinary daily output of fistula bile in man may be increased from 500 cc. to more than 1,000 cc. (Gundermann). Disease itself probably does not increase the bile. In the literature of the ancients, the presence of jaundice probably initiated the idea of excess bile, which in reality was retained bile with decreased production.

ACHOLIA

The absence of bile was described by Frerichs as the so-called "white bile." The liver fails to secrete a bile containing bile salts and pigment but does contain an abundance of mucus and cholesterol. Berg did not find obstruction of the extrahepatic bile ducts in all cases. White bile is dealt with in the chapter on "Toxicity of Other Constituents of Bile."

SPECIAL SYMPTOMS OF JAUNDICE

PRURITUS

Pruritus, as early as Hippocrates, has been associated with jaundice. It is now held to occur in 60–70 per cent of icteric cases, both male and female. Several representations of its frequency have been given, varying from 50 per cent (Cabot, 309) to 60 per cent when there are stones in the common duct, greater still with stricture of the duct, and 75 per cent with neoplastic diseases causing obstruction (Murchison). Intol-

erable pruritus often precedes a definite appearance of jaundice, according to Judd. However, it has been found but rarely except in obstruction of the common duct (Murchison). Preicteric itching frequently accompanies cases of obstruction of the common duct, owing to neoplastic diseases (Riesman), while in hemolytic jaundice there is no itching.

Moynihan (1323) said: "Almost every patient will declare that the relief from the maddening torture of itching is worth every sacrifice." In most cases there is no other disturbance of the skin than itching, but occasionally pimples or pustules appear. These may be secondary to the scratching, followed by infection. Urticaria rarely occurs. This itching has been reported as occurring from a few days to a few months before the actual pigmentation of the skin or sclera (Riesman, Graves) without other premonitory symptoms. Where there is a total obstruction, it is more common than bradycardia. It is at times very annoying in acute catarrhal jaundice, where it usually occurs early in the course of the disease, bleeding occurring late.

In the investigation of the causes, bile pigment was considered. Pruritus occurred without jaundice, and there was a normal quantity of bile pigment which gave the direct van den Bergh reaction (McVicar). It was observed again in early obstructive jaundice where the bilirubin concentration was normal. Thus, pruritus may occur with a normal concentration of bilirubin in the blood. Very severe cases of jaundice are frequently observed with a high van den Bergh reaction and no itching of the skin. Thus, the itching cannot be attributed to the pigment, and bears no relation to the quantity of it (Graves, Quincke, Rolleston, and Frerichs). The intensity of the itching bears no constant relation to the anticipatory degree of pigmentation. It is not pathognomonic. In a case with an injection of pigment into the blood stream of 1 gm. to 800 cc. of blood, there was no itching (Chabrol). These results, though, are defective in that the bile salts and pigments of a normal person are more rapidly eliminated than

in a jaundiced person. However, the injection did not cause pruritus.

In determining the influence of bile salts, the Pettenkofer reactions were not always positive. Values ranged from 5.1 to 15.3 mm. per 100 cc. of blood in patients with nonobstructive jaundice and no pruritus, while values of 5.5–8.7 were found in cases of liver disease with pruritus and no jaundice. A value of 16.3 was observed in a patient with liver disease and obstructive jaundice with pruritus. Also, a 3.5 value was obtained in a case of nonobstructive jaundice with pruritus (Rowntree, Greene, and Aldrich). An intravenous injection in man of 2–3 gm. of bile salts did not cause pruritus in spite of the increase in concentration of bile salts in the blood to 0.50 gm. per liter, i.e., a concentration five times the greatest bile-salt retention observed in complete obstruction of the common duct (maximum). Furthermore, an injection of bile salts brought relief in a case of chronic vesiculo-erythematous eruption with intense itching. Thus, pruritus may occur with high Pettenkofer values or with a normal quantity of bile acids in the blood. This disproves the theory of the French school, and generally held today, that pruritus is due to bile salts.

Likewise, pruritus of jaundice has no relation to the isomer of bilirubin, namely, hematoporphyrin, which causes itching in the daytime soon after the skin has been exposed to the sunlight. Pruritus of jaundice occurs at night when the skin is covered, and sunlight has no effect on its intensity. In addition, it has no relation to the cholesterol in the blood (Snell) or porphyrin (Rosenthal). Neither is it a question of carbohydrates affecting the nerves (Lichtman).

It has been suggested that pruritus is due to the failure of liver metabolism. In certain cases of persistent itching without jaundice there is a decreased ability of the liver to excrete phenoltetrachlorophthalein. Thus, pruritus is associated with a disturbed hepatic function (McVicar).

Does the absence of bile from the intestine permit the pro-

duction, and also the absorption, of abnormal substances which cause a reaction similar to the urticaria from strawberries? The retention of metabolic poisons normally excreted in the bile by the liver may cause the pruritus, but we do not have sufficient evidence on this subject.

As for treatment, complete relief often is obtained following drainage of the gallbladder even before the blood bile returns to normal. It has also been suggested¹ that the most efficient treatment is to get rid of the icterus. However, since this symptom cannot be reproduced in experimental animals, the etiology must be investigated in man, an unfortunate situation with regard to this research.

XANTHOMA

The presence of xanthoma in chronic jaundice, according to Hewlett, indicates that there is some alteration in the metabolism of cholesterol, since these yellow tumors contain fairly large cholesterol deposits. Other terms used for xanthelasma are *molluscum cholestérique* and *xanthoma diabeticorum*. Small yellowish lesions frequently appear about the eyelids, and at times are found distributed over the body. These vary in color from lemon or orange to a deep brown. Jaundice is associated with xanthoma, according to Stelwagon, in 23 out of 28 adult cases. Xanthoma diabeticorum is associated with liver disfunction. The symptoms are those of a small tumor, and there may be itching.

Cholesterol in the normal blood serum averages 0.16 per cent but is usually increased in chronic jaundice. The color in the tumors is due to bile or blood pigment. Palmer has shown that orange, red, and yellow pigments in animals and plants are due to carotinoids, carotin, and xanthophyll. White body fat is found in hogs, sheep, dogs, and cats; and there are no pigments in the blood serum. In cattle, blood serum, fat and butter, are colored with carotin, which is derived from the food. In the hen, the egg yolk and fat are due to xanthophyll, derived from food.

¹ *JAMA*, 92:830, 1929.

This involves also the question of the relation of plant pigment and animal pigments, such as hemoglobin and bile pigments. Some of the structural formulas are very closely related; there also is a similarity in the reaction to sunlight.

With this large number of pigments causing pigmentation of various body tissues, it is impossible at the present time to incriminate bilirubin definitely.

YELLOW VISION

Xanthopsia, yellow vision, rarely occurs. Lucretius appeared to have observed it: "*Lurida praeterea fiunt quaecumque videntur arquatis.*" Galen, Sydenham, and Legg have also observed this condition. Frerichs (634, 1:108) never had an opportunity of seeing a case, although he always made inquiries on the point. Yellow vision usually occurs only in those patients who have been jaundiced for a long time. There are a number of other conditions which give yellow vision, such as an overdose of santonin, which Frerichs said is due to the medicine in the blood stream; and likewise yellow vision in jaundice is due to bile pigment in the blood stream. The patients complain of normally white objects appearing yellow. Some complain of all objects having a yellowish border. The humors of the eye may be colored with bilirubin. This change in vision is probably similar to the yellow vision produced by santonin. The writer had, on one occasion, intense orange-yellow vision following the use of santonin. Xanthopsia may be present only a few hours, or it may continue for days. It frequently disappears before the skin has lost its yellowish color.

THE LIVER IN JAUNDICE

With the obstruction to the outflow of bile, impairment of liver function begins immediately and is progressive so long as the obstruction exists. The cause of this deficiency and its course and effect on the body should be sought. It is obvious that, unless the destruction has progressed too far, the proc-

ess is reversible, for with release of the obstruction the liver returns again to normal function.

There are a large number of conditions which cause jaundice. All have one common symptom, that is, the retention of bile pigment. Either more pigment is thrown into the blood than is usual or the levels of the portals of exit have been raised. Essentially, then, there is a failure of excretion. Since the liver is the principal excretory organ for bile pigment, one can only conclude, upon the appearance of jaundice, that the liver does not excrete an adequate amount of bile. From this method of reasoning, one finds dyscholia, or even acholia, entirely possible as far as the liver is concerned. But it is necessary, then, to know the source of all the constituents of bile to determine whether the liver is only a selective excretory organ or the real manufacturer or transformer of the various substances in bile. If the liver only selectively removes these substances from the blood stream and does not manufacture them chemically, then in any retention jaundice the toxic substances in the bile will accumulate in the blood stream and in other tissues. If the liver manufactures or transforms or alters these substances, at least in part, then there may be a toxicity caused by hepatic failure.

The evidence so far given seems to favor a multiplicity of functions for the liver, such as, extractor of poisons from the blood, detoxifier, and manufacturer.

That there is actual liver involvement, according to Brakefield and Schmidt, has been shown by the decreased ability of the liver, in dogs with obstruction of the common duct, to synthesize hippuric acid or detoxify benzoic acid by conjugation.

Microscopic evidence is also available if an examination is made of the livers of dogs following obstruction of the common duct. In the liver of a dog with obstruction for 4 weeks, the trabeculae are slightly distorted and the bile ducts are swollen; with obstruction for 11 weeks, the trabeculae are considerably distorted and many of the cells are broken

down, the interlobular connective tissue is increased, and there are large biliary thrombi around broad spaces, also a great number of giant cells.

An extensive study of the liver in obstructive and toxic jaundice was made by Ogato. The cirrhotic altering after ligation of the common duct was different from the toxic type. In the latter there was considerable connective tissue proliferation in addition to the deterioration of the parenchyma. There was a tissue increase in the bile passages, and connective tissue appeared, which was not a regeneration process after necrosis of the parenchyma but was an independent process through the stimulation of the dammed-up bile in the passages. In rats the ducts and connective tissue increase was principally intralobular; while in other animals, namely, the rabbit, guinea-pig and dog, it was interlobular.

The usual theory of the pathogenesis of icterus does not include all the possibilities. In the earliest stage of stasis icterus there has been an alteration along the bile capillaries because the jaundice has already appeared before there is any evidence of rupture of the capillaries or even thrombosis. There are, then, two phases of obstructive jaundice: first, *ectasia*, the bile capillaries are altered, permitting fluid bile to pass by filtration into the perivascular lymph stream or blood stream; second, the bile capillaries are ruptured, permitting the expulsion of bile, which is later inspissated, causing a precipitate formation. This second phase is important: the formation of bile casts in many animals, such as the small rodents, is entirely absent, although in these animals a reaction of the bile passage increases to a surprising extent, in contrast to the necrosis in dog and man. Similar observations of obstructive jaundice have been made in different animals. In icterogen poisoning, bile stasis seems to play no role. The appearance of the icterus must be explained as a functional disturbance of the liver or as of hematogenous origin.

Simple icterus or icterus caused by bacterial infection or

chloroform poisoning has caused no plain cirrhotic alterations, although some of the investigations would point that way. The failure of such changes in opposition to the unmistakable progressive alteration in the obstructive jaundice and the icterogen poisoning depends entirely on a quicker appearance of the melting-down of the trellis vascular structure in the necrotic center.

A study of icteric livers, with specific regard for liver cells, the meshwork of reticulum fibers, and the reconstruction of damaged trabeculae, was made by Schwarz (1734). Of the 20 cases with biliary thrombi, 7 were studied in detail. All had mechanical icterus, and the destructive changes were caused by the retention of bile. Stasis produced dilatation of the bile capillaries and tears in the intercellular and intracellular endings of the fine biliary vessels. Thrombi formed casts within the capillaries and became coiled; the bile diffused into the surrounding tissue; and a fine, granular precipitate occurred within the liver cells. Trabeculae became irregular; leukocytes were scarce; and the destroyed liver cells were replaced by new ones. Connective tissue strands slowly invaded, evidently from the edges of the acini.

According to some observers, human bile is incapable of causing any permanent hepatic injury. If this be true, man differs from all other animals which have been well studied, for in these, without exception, aseptic bile stasis results in important local changes. In man, however, death usually occurs before cirrhotic changes are manifest. Biliary obstruction undoubtedly produces changes in the liver. Clinical jaundice is certainly not due to local liver lesion but to generalized injury to the hepatic parenchyma or ducts or to blood destruction.

Some regeneration of the sections of the liver following ligation was observed by Richardson. There was invasion of the necrotic areas by columns of liver cells. Gradual shrinkage in the size of the liver lobules pointed to a disturbed function of the cell and a damming-back of toxic bile. These were

handicaps too great for the parenchymatous cells to overcome. Some of the changes which occurred in the liver may have been caused by the action of bacteria, which in turn caused the jaundice. The term *aseptic bile* is a relative term, as the liver bile and gallbladder bile have been shown frequently to contain various kinds of bacteria (Judd). The mere presence of bacteria does not indicate that they are the actual producers of the pathologic conditions.

Bile given by mouth, and entering the stomach, small, or large intestine, causes a definitely increased secretion of the liver, according to Stadelmann (1826). It acts on the liver as a stimulant (*stärkere Reizwirkung*). If a greater amount acts on the liver, there is a question as to how much strong stimuli can be brought into play before actual damage to the liver begins. Leyden found that bile salts injected intravenously act as a poison on the liver, causing fatty degeneration of the liver cells. Saadi-Nazim and Uselli presented a rather interesting theory that the hepatic cells have a double action: *glycogénétique* and a *glycogenolytique*, which are reversible. In animals without a pancreas, the formation of glycogen is not possible, since the liver cannot obtain more insulin; but the act of liberation of glycogen is substituted. Their second theory held that intravenous bile stimulates both hepatic and pancreatic cells. The insulin of the pancreas tends to diminish the blood sugar, thus keeping the blood sugar a constant, sometimes causing it to fall below the normal. Following removal of the pancreas, the bile acts only on the liver, thus increasing the blood sugar. It was further observed that intravenous bile causes these same dogs with a cannula in the common duct to secrete a larger amount of bile.

The various causes of serious symptoms of jaundice were listed by Bouchard: biliary poisoning, causing cholemia; cell destruction with hepatic alteration; liver atrophy and suppression of function, causing acholia; renal changes, followed by inadequacy; and self-poisoning, with failure to eliminate normal toxic products. In malignant jaundice there is an in-

terference with liver function, followed by alteration of the kidneys and then of all the other tissues of the body.

When the liver can no longer go on with metabolism and can no longer detoxify substances, is it able to continue to manufacture bile pigments and bile salts? Bouchard thought that when this state is reached it is principally the bile that causes the increase in the intoxication. He did not think his ideas of malignant jaundice applied entirely to the acute yellow atrophy of Rokitansky; the severe jaundice of Ozanam; the typhoid jaundice of Leberet; the essential hemorrhagic jaundice of Monneret; or the grave essential jaundice of Beneuvre. His ideas applied to simple jaundice that becomes more and more severe. The liver finally reaches the stage where it no longer makes bile; yet it is not the acholia that kills the patients; instead, the liver no longer detoxifies and the kidneys fail to excrete the poison. The greatest danger in jaundice is renal impermeability. Severe jaundice might be cured if the kidneys could remain permeable. He believed that the coloring matter does not kill in black jaundice because it becomes fixed by the tissues. He also thought that the pigment is ten times more toxic than the bile salts.

Jaundice theories.—Frerichs thought there is a suppression of the liver's power of disassimilation (acholia). Buhl believed that jaundice is the result of cerebral edema, because of the failure of the bile to eliminate water; of suppressed hepatic function of short duration; of polycholia of short duration; and of uremia. Bouchard concurred with Frerichs.

HEPATIC INSUFFICIENCY

Hepatic insufficiency may result from complete occlusion of the bile ducts or complete cessation of liver activity without obstruction. There is too much argument about this point for discussion here, except to say that, when a complete hepatectomy is done, the animal survives for only a few hours. Mann and his co-workers have shown that a very

large portion of liver tissue can be excised and the animals continue to live, and that there is actual regeneration of new liver tissue, replacing that which had been lost. There is an actual change in the bile secretion following the administration of chloroform to dogs (Drury and Rous); the amount of bile is decreased; likewise, the amount of pigment and cholesterol is lessened to the extent of being found only in very small quantities in the bile. If the amount of chloroform is sufficient to cause death by the third day, the bile becomes a thin, clear fluid entirely free from bile acids. This is one instance where there is an actual suppression of the secretion (or excretion) of bile, probably because of actual impairment of the hepatic cells. When a sublethal amount of chloroform is used, there is a greater amount of bile pigment in the bile, owing to blood destruction caused by the chloroform anesthesia.

In hepatic insufficiency there is a fall in blood pressure, a slowing of the pulse, itching, albuminuria with renal irritation, and a disturbed acid-base equilibrium. All of these, according to the old view, are caused by bile salts. The degree of the symptoms bears no relation to the concentration of bile salts in the blood. The itching, increased bleeding time, and jaundice are present when the bile salts are normal. Injection of bile salts does not reproduce these symptoms.

In cholemic hepatitis (Walters [2041]), there is paling and a thinning of the bile (man with external fistula); the amount of the bile increases (cholerrhagia); the patient becomes weaker, pulse weaker, temperature subnormal; there is restlessness, greater fatigue, and vomiting; the jaundice does not increase but the pallor does; the urine volume is in proportion to fluid intake; and the blood urea remains low. Autopsy reveals: biliary thrombi in the liver, hepatic cells shrunk, and fibrosis of the portal areas.

The hepatic insufficiency may be compared with hepatectomy, which is followed by hypoglycemia, cessation of urea formation, increase in uric acid and amino acids in the blood.

However, the cause of the symptoms of liver deficiency cannot be assigned to amino acids, as they are nontoxic, as shown by Newburgh and Marsh, who injected 2-4 gm. per kilogram with no symptoms; polypeptides are equally harmless, as shown by Jackson; and the glycogen starvation is certainly not responsible for all the symptoms.

The most frequent causes of death in jaundice are: hemorrhage, uremia, and hepatic insufficiency.

RÉSUMÉ

The symptoms and signs due to the retention of bile and the clinical appearance of jaundice may overshadow the unseen factors back of the jaundice or the accompanying conditions. The intoxication produced by the retention of bile is accompanied by a long train of conditions. Only a small portion of these effects can be attributed to bile itself.

Jaundice is a symptom, not a disease.

CHAPTER XXIII

PHYSIOLOGIC JAUNDICE

ICTERUS NEONATORUM

THE perceptible evidence of jaundice in the new-born usually appears a few days after birth, in contrast with the earlier appearance in congenital obstructive jaundice. This type of jaundice is present, using visible evidence as the criterion, in from 40 to 80 per cent of the new-born (Marfan). Spectroscopic examination of the blood shows a much greater percentage of cases with increased bilirubin. The delay in its appearance has been ascribed to the greater storage capacity of the relatively large size of the infant liver; also, the bilirubin has an extrahepatic origin, taking longer to arrive at its normal portal of exit and to reach the superabundant circulating amount necessary to produce pigmentation in the tissues. Metzger (1272) observed jaundice in 504 out of 4,000 new-born calves; it was present in 24 out of 322 examined soon after birth. It persisted for days or weeks after the calf was born. Icterus in man is usually not present at birth but does occur 24-48 hours afterward, with first a slight tinging of the conjunctiva and finally a deep-orange coloring of the skin in extreme cases. A number of theories have been offered to explain the causes of jaundice of the new-born. Birch-Hirschfeld has reviewed these: change in the circulation at birth, with edema of liver; compression of the bile passages; hematogenous origin; catarrhal condition; and infection of the navel, with phlebitis. Hess found little bile in the duodenum the first 36 hours, but excessive amounts of bile in the stomach and duodenum in infants with marked jaundice. He accordingly concluded that the new burden placed on the liver is too

great for it to cope with and that therefore there is a retention of the excess bile in the blood.

The hematogenous theory, that there is an actual destruction of erythrocytes, has many supporters. The fragility of the red blood cells in saline solution is, for the minimum, 50-52. The number of red cells in the new-born is about 7,000,000, and in a few days decreases to 5,000,000 (Lereboullet), thus setting free a large quantity of hemoglobin. Because there are bile salts in the blood and urine in congenital icterus, Stengel concluded that the jaundice is of hepatic origin rather than of purely hematogenous origin. Since the blood of the new-born contains an excess of bilirubin, Hellmuth concluded that icterus neonatorum is of hemolytic origin. Bilirubin has been crystallized from the blood and from peritoneal and pericardial fluids in the new-born with icterus. Crystals appear in the blood and tissues after death. Wandering cells in the peritoneal fluid engulf bilirubin crystals. Bile pigment infarcts occur in the kidneys. Icterus neonatorum gives only the indirect van den Bergh test. Aschoff and Hummel (84) formed the opinion that in this disease bile pigments are formed from the tissues outside the liver. From spectroscopic studies, Ylppö concluded that the jaundice is due to greater bile formation in the liver before or after birth, with passage of the pigment into the blood stream. Stengel supported this view, basing it on the assumption that purely hematogenous jaundice should not present an excess of bile salts.

The direct relation of the iron contents of the placenta and the bilirubinemia and the jaundice of the new-born is due to the hemolysis, fetal or maternal, in the placenta (Williamson). Kramer found bilirubin in the blood of the umbilical cord in quantities from 1:28,000 to 1:140,000; the average, 1:46,000. The indirect van den Bergh reaction is very definite. In 100 new-born tested, the direct reaction was not observed. All with 1:36,000 or more were definitely jaundiced. From these findings Kramer concluded that icterus neona-

torum is not mechanical. He suggested that it is due to a destruction of the surplus red blood cells (fetal or maternal). The new-born contains a large surplus of both red cell and iron reserve. During pregnancy the serum bilirubin which is diffusible is increased in the mother, and there will likewise be an increase in the blood of the fetus. It is probable that there are several factors involved in the production of icterus neonatorum.

Bilirubinemia was found in each of 34 new-born infants examined by Bang (109). The fetal bilirubin may increase after birth if there has been obstetric trauma, the increase being due to absorption of bilirubin from the extravasated blood. He concluded that the ordinary jaundice of the newly born is not a disease but a physiologic condition. Likewise he observed bilirubinemia in patients with extrauterine pregnancies; with fractures and contusions; following operations; and, in fact, in any patient with recently extravasated blood. The symptoms are usually mild; the feces normal; the pulse normal; the urine may contain cells inclosing bilirubin crystals; and the van den Bergh test gives an indirect reaction and shows an increase of bilirubin in the blood. The skin is yellow, and the sclerae may be normal or may later turn yellow. If the jaundice is prolonged, the temporary teeth may be colored green (Abt).

There is considerable evidence to support the theory that before and at birth there is a large amount of bile pigment in the blood.

ICTERUS GRAVIDA

Pregnancy is accompanied by a biliary retention, with emphasis on cholesterol, bile salts, and bilirubin (Chabrol, 337). There is an increased pigmentation of the face, called the "mask of pregnancy"; also of the body, neck, and nipples. Gilbert evaluated the average bilirubin in the blood during pregnancy at 1:30,000. The bile salts were increased in the urine, according to Brulé. Gallstone attacks are frequently seen during or just after pregnancy.

CHAPTER XXIV

JAUNDICE CAUSED BY EXTRAHEPATIC OBSTRUCTION

CONGENITAL ATRESIA OF THE BILE DUCTS

CONGENITAL atresia of the bile ducts causes jaundice to develop soon after birth. There is an obstruction to the flow of bile from the liver to the intestine. Up to the present time only 170 cases have been reported (Phillips). Most of these have been verified by operation or autopsy. Many theories have been advanced to explain why the lumen of the duct becomes occluded. If the complete obliteration does not occur until after birth, the effect of bile retention in the system cannot be so accurately determined and the time factor will also be variable.

The symptoms are due to the retention of bile in the body and also to its absence from the intestine, causing malnutrition from defective absorption of foods. The jaundice may be present at birth or may appear within 10 days to 2 weeks. If the jaundice appears immediately, it is more likely to be due to icterus neonatorum. The liver probably stores some of the bile pigment; and accordingly it does not appear in the blood serum, skin, or conjunctivae until the storage space is overloaded. At this time bile pigment can be found in increasing quantities in the blood, which gives the direct van den Bergh reaction. Only one case has been reported which gave only the indirect reaction (Feldman and Lawson). The direct van den Bergh reaction is thought to be present in hemolytic jaundice only. Bile salts may also appear in the blood serum. The temporary teeth may be yellowish, but in long-standing cases are frequently green. The stools are usually greasy white and contain neither bile pigment nor bile acids. Meconium is nor-

mally brownish green, owing to bile pigment. Slightly colored stools in cases of complete atresia may be due to the pigmentation in the intestinal secretions rather than to bile passing by the normal channel into the intestine. The urine usually is very highly colored, and bile salts have been observed (Stengel). Cells containing crystalline bilirubin have been observed frequently in the urine. The skin is usually yellowish, but in long-standing cases may be greenish in color. Hemorrhages are very frequently observed in the skin or from the mucous membrane. The coagulation time of the blood is greatly lengthened. The nitrogen metabolism is normal. The heart rate is frequently slow; some clinicians, however, have failed to observe a slow pulse.

Bile is absent from the intestine; and since it is an essential aid to digestion, the absorption of food from the intestine is greatly diminished. The pancreatic duct is frequently occluded also; so the absence of the combined action of bile and pancreatic juice, particularly on the fats in the intestine, causes a low fat absorption. The calcium intake, which depends on the presence of bile salts for its absorption, is likewise diminished.

The length of life of unoperated infants with complete atresia is about 10 weeks; very few live beyond 8 months (6 months, Cole). A few cases have been reported which have lived for several years. Those living longer may have anomalous small ducts or only a partial obstruction. The question of the length of life following complete biliary obstruction is found in another section in this chapter. Death has been attributed to the toxic action of the accumulated bile acids in the body tissues. These acids are not entirely eliminated by the urine or by other body secretions but may actually be retained in the various body cells to such an extent that the cells themselves become overburdened and unable to metabolize their own food satisfactorily. Certainly there is malnutrition from inability to absorb food properly from the gastrointestinal tract. When the general nutrition suffers, ex-

haustion appears. Death usually occurs in the first few months, frequently from hemorrhages.

All of these cases of congenital atresia are fatal unless operation is performed so that bile passes into the intestine. Ladd operated on 11 patients, with 6 recoveries.

The cause of death of infants with atresia of the bile ducts cannot, with our present data, be assigned directly and completely to the toxicity of bile itself. No experimental data are available on ligation of the common duct immediately following birth of lower forms of animals.

In more than 16 per cent of all reported cases of congenital atresia Holmes found the hepatic and cystic ducts normal. The surgical procedure would then be a cholecystenterostomy. Most of the patients do not come to operation until the obstructive jaundice has reached an advanced state. Only a few of the infants that have been operated on have survived. Hemorrhage is an exceedingly grave factor.

Congenital absence of the gallbladder is more common than atresia of the bile ducts, while an anomalous biliary tract occurs in about 10 per cent of all persons (Mentzer).

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

Obstruction of the bile ducts has been known, for many centuries, to be associated with jaundice. Frequently at autopsy calculi have been found in the ducts; and the jaundice was looked upon as a result of the suppression of excretion of bile, because the ducts were already filled with bile (Sannert in 1655). The excretory power of the liver cells was blocked by the dammed-up bile. The first experimental investigation of this doctrine was made by Saunders in 1795, when he ligated the bile duct of a dog, which was killed 2 hours later. Bile-stained fluid was found about the thoracic duct; paper was stained yellow by the blood serum from the jugular vein, but the paper was stained a deeper yellow by the serum from the hepatic vein. He evidently ligated the hepatic duct, for jaundice appears much later following ligation of the common

duct with the gallbladder intact. This work was repeated by Brodie, the surgeon, in 1823. A silk ligature was applied around the common bile duct of a calf, completely preventing bile from entering the intestine. This experiment was repeated on a number of animals; all were allowed to live. The results were always the same: jaundice appeared, the tunicae conjunctivae of the eyes were tinged with bile, and the urine was seen to contain bile. Extreme emaciation was found in cats similar to that in man.

Brodie wrote: "The fact of individuals having occasionally lived for a few weeks or months under these circumstances only proved that nutrition may take place to some extent without chyle being formed. In my experiments I found that the more fluid parts of the chyme had been absorbed, and probably this would have been sufficient to maintain life during a limited period. These experiments are sufficient to prove that the office of the bile is to change the nutritious part of the chyme into chyle and to separate from it the excrementitious matter."

He concluded from his experiments that bile is toxic. His work created considerable interest in the scientific world. This was followed by the work of Tiedmann and Gmelin (1929) in 1824, who recorded the following symptoms due to ligation of the common duct: vomiting, loss of appetite, increase of thirst, jaundice, and diminution of the symptoms within a few days after the canal re-established itself. This spontaneous canalization happened in one of the dogs. Thus was definitely established the association of obstruction of the common duct with jaundice.

Among the early workers and writers were: Boerhaave, about 1700; Autenrieth, 1802; Eaglesfield Smith, 1805; H. Mayo, 1826; Voisin, 1833; Werner, 1834; Prout, 1834; and Blondlot, 1846.

In Harley's experiments (767) in 1892 both the common bile duct and thoracic duct of dogs were ligated. In another set of experiments the common bile duct was ligated first and

later the thoracic duct; altogether he used 20 dogs. He drew the following conclusions from his experimental work. Bile which is eliminated in the urine or deposited in the skin in cases of obstructive jaundice does not find its way into the general circulation through being absorbed by the blood capillaries. In obstructive jaundice the lymphatics absorb the bile, which goes by way of the thoracic duct into the general circulation. If jaundice appears after ligation of both the common and thoracic ducts, a collateral lymphatic circulation has been set up.

He made an analysis of bile in the gallbladder before and after ligation of both the common bile duct and thoracic duct. The mucin increased from 0.738 to 1.890 per cent; the fat and lecithin decreased slightly; the cholesterol increased markedly from 0.034 to 0.557 per cent; and the sodium taurocholate decreased from 12.689 to 10.055 per cent. The less soluble constituents of bile, such as cholesterol and mucin, were most concentrated; ligation of the thoracic duct not only prevented obstructive jaundice but checked it even after it had set in.

The relation of obstruction of the common duct to jaundice in the dog was shown by Haberland. When there was no infection of the bile ducts, the dogs gave no evidence of abnormality for the first 4 weeks. Bile pigment appeared in the blood and urine 12 hours after the operation. The skin did not become yellow. The highest serum bilirubin was only 1.43 mg. per 100 cc., as the kidneys of the dog have a very low threshold value for bilirubin. After 4 weeks, symptoms began to appear and gradually became very severe: cirrhosis of the liver, ascites, cachexia, heart weakness, and general intoxication. The skin finally became yellow.

Following ligation of the common duct in dogs the bilirubin, bile salts, and cholesterol increase in the blood (Varela and Rubino). Bilirubin increases gradually and reaches a maximum in 3-7 days and continues high. The bile salts increase to five or six times their original level and reach a

maximum in 7 or 8 days; then gradually return to their previous normal level, which varies. Cholesterol decreases; then may increase one or two times and then decrease. The variations in the serum bilirubin in cats parallel the pathologic changes in the liver for about 2 weeks; then there is no constant relationship (Cantarow and Stewart). The diazo reaction is positive after 27-48 hours in dog's serum (Oka).

Following obstruction of the common duct the liver is affected, the bile passages dilate, the parenchyma is encroached upon, and the hepatic tissue gradually ceases to function. A comparable series of changes takes place in dehepatized dogs: the blood sugar is lowered; the uric acid in the blood is increased; and the amino acids are not metabolized. Thus the deamidization, and consequently detoxification, is prevented.

The dilatation of the bile ducts in man was found at autopsy, by Counseller and McIndoe, to be in proportion to the length of time of obstruction of the ducts and also to the degree of the obstruction. Complete obstruction showed dilatation of the terminal filaments. Hepatic parenchyma was atrophied in proportion to the dilatation of the ducts, probably resulting from pressure of bile.

Obstruction of a small portion of the liver is followed by complete parenchymal atrophy of that part. Common duct occlusion may cause death before demonstrable changes have had time to take place in the liver (Judd and Burden [948]).

It would appear that the toxicity of obstructive jaundice may be extremely complicated, involving all the functions of the liver. The toxicity to some extent, but certainly not entirely, may depend on the presence of accumulated bile antecedents and bile constituents in the organism.

The effects on the liver of sudden occlusion of the common duct in experimental animals cannot be compared very closely with the human obstruction by gallstones, for it may be that gallstones are associated with, or precipitated by, infection in the bile passages or gallbladder.

Moynihan in 1926 made the statement, "No one living is infallible in the differential diagnosis of obstructive jaundice."

LENGTH OF LIFE WITH OBSTRUCTION OF THE COMMON DUCT

In man it is difficult to determine just when obstruction actually occurs, when it becomes partial, or when it is complete. In experimental animals a ligature placed about the common duct often becomes included within a mass of new tissue, and a new canal forms about it, making a completely open passage for the bile, identical with the old common duct. The ability of an animal to replace its common bile duct may lead to a large amount of confusion and misinterpretation. In experimental work to obviate this recanalization of the common duct, it has become customary to apply a double ligature about the common duct and to sever the duct between the ligatures, or even to remove a section of the duct for examination. Again, anomalous bile ducts are so common in man and lower animals that occasionally they could cause erroneous interpretations through failure of recognition even at autopsy. Even one of these multiple ducts may carry enough bile from the liver to the intestine to cause serious misinterpretation, especially when it is remembered that only a small portion of the liver is absolutely essential to life, and also that Mann's partially hepatectomized animals very rapidly replaced the removed liver tissue. An excellent review on these anomalies by Mentzer (1268) in 1929 was very timely.

A woman with complete obstruction of the common duct for $3\frac{1}{2}$ years, according to Wangenstein (2051), died following an operation at which no extrahepatic ducts were found. Autopsy showed complete obliteration of the ducts. Jaundice of 16 years' duration in a woman nineteen years old has been reported by Treves. At operation a complete fibrous obliteration of the common duct was found. A cholecystenterostomy

was done, and the patient was still living 10 months later. Most patients die within the first 6 months following complete obstruction.

Dogs usually live 40-65 days following occlusion and severance of the common duct (Haberland). Mann, using a low protein diet, increased the length of life. Of the smaller animals: rabbits (Gerhardt [670]) survive 3-10 days, maximum 31 days; rabbit (Haberland), 34 days; guinea-pigs (Steinhaus), not more than 10 days; mouse, 9 days; rats, 23 days; cat, 41 days (Haberland). Still and Carlson (1842), following ligation of the common duct, reported that one dog lived 206 days, which is the longest time yet recorded.

It is generally conceded that the average length of life following continuous obstructive jaundice is not more than 6 months. Some patients may live much longer, but it is doubtful whether there has been a complete obstruction ever since the appearance of jaundice. Autopsy frequently discloses a partial obstruction of the common duct with jaundice. It appears that benign obstruction, such as stricture following operation, will gradually close the lumen of the duct. If only a small amount of bile passes through into the intestine, the length of life will be greatly prolonged.

The usual cause of death is not the toxic bile substances but some primary pathologic condition, such as sarcoma of the liver or carcinoma of some structure pressing on or involving the bile passages. If the obstruction is due to a benign condition, a low meat diet usually prolongs life beyond the ordinary prognosis.

SURGICAL RISK IN JAUNDICE AND PRE- OPERATIVE TREATMENT

Operations on patients with obstructive jaundice offer three avenues of danger, aside from the so-called "accidents" of surgery: hemorrhage, uremia, and hepatic insufficiency (Walters [2041]).

With hepatic insufficiency, jaundice increases, the coagula-

tion time of the blood is lengthened, and the blood urea increases until the patient goes into uremic coma. The surgical risk is from oozing of blood rather than from hemorrhage of large vessels. The toxemia is due to the increased nonprotein nitrogen in the blood. Hepatic insufficiency is accompanied by deficiency of glycogen.

In some cases the action of calcium chloride on the coagulation of the blood has been very transient. It is necessary in these cases to operate within the period of time when the coagulation time is most greatly diminished. Blood transfusions may diminish the coagulation time of blood for 8 hours.

The mortality of operation on deeply jaundiced patients was 65-75 per cent before recent methods were developed, such as intravenous injections of calcium chloride, blood transfusions, quantitative bilirubin estimations in the blood, including observations of its fluctuation and renal function tests. Now the risk of operation on all patients with jaundice in the Mayo Clinic is below 10 per cent (Walters and McVicar [2046]).

At times intravenous calcium by the Lee and Vincent method fails to reduce the blood-clotting time. When this method fails, transfusions are imperative. Calcium chloride, 10 per cent, given intravenously on three successive days, often reduces the time from 30 minutes to normal (Walters). An actual deficiency in calcium in the blood stream has not been demonstrated in jaundice. There seems to be some difference in the reaction of the jaundiced dog and the normal dog to toxic doses of calcium. The work of Emerson (531) showed that the average lethal dose of bile given intravenously at a given rate, until death occurred, was 8.75 cc. per pound of dog for 7 dogs, as compared with 7.50 cc. of bile and 5 per cent calcium chloride for 19 dogs. He concluded that calcium does not protect against the toxicity of bile.

Horrall found that calcium chloride, added to bile and bile salts in various proportions prior to intravenous or intraperitoneal injections, not only does not protect against the bile

but increases the toxicity, causing death with smaller amounts of bile and within a shorter time following the injections.

A few hours before operation the preparatory treatment should consist of rest, increased fluid intake, adequate glucose administration, and sufficient calcium or blood transfusion to cause a diminished coagulation time of the blood to near normal. Finsterer (582) advised irradiation of the spleen immediately preceding operation on jaundiced patients, as a preventive of cholemic hemorrhages. If given 24 hours previously, it has little or no value, as the effect has worn away. The precise action of the Roentgen rays was not explained.

CHAPTER XXV

BILE LOSS: EXTERNAL BILIARY FISTULA AND LENGTH OF LIFE

THIS chapter has to do with the free passage of bile to the exterior by way of a fistulous tract, with partial or complete loss of all bile constituents, and the conditions resulting from the feeding of bile.

The harm that can come from bile may be due to either its presence or its absence; but the writer has assumed in this monograph that in most instances the toxicity of bile refers to the presence of bile, its excess, wrong location, or action under pressure, one exception being where bile is lost through an external biliary fistula. The absence of bile is followed by a certain series of symptoms, such as those which are associated with a permanent biliary fistula.

The related abnormalities to bile fistulas are: (1) intestinal disturbances, with loss of weight; (2) spontaneous bleeding and anemia; (3) spontaneous fractures and bone abnormalities; (4) duodenal ulcers; and (5) cholelithiasis, with obstruction of the fistulous tract (Hawkins and Whipple). Permanent biliary fistula in dog causes a decrease in blood calcium and phosphates, a marked decrease in alkali reserve, and an increased output of calcium in the bile (Cavazza). The hypocalcemia frequently causes tetanic symptoms (Heymann). Removal of the parathyroids influences the electrolytic content of the blood in biliary fistula (Nicolosi, Rabboni) and diminishes the output in the bile (Tuzioka).

Other factors are recorded under the discussion of cholemic hemorrhage, chapter xi.

Infection of the gallbladder and biliary tract usually occurs in animals with an external biliary fistula but may not seriously impair the health of the animal. Experimental ex-

ternal sterile fistulas have been prepared in dogs by Rous and McMaster. Bile output of these dogs, even with fasting, could not be reduced below 30-40 mg. of bile salt per kilogram of body weight per 24 hours, as determined by the amino-nitrogen method for measuring the bile salt in terms of taurocholic acid.

Continuous external drainage of bile causes rapid loss of weight and cannot continue indefinitely. Experimental evidence has shown that if animals lose all their bile they will live only a few weeks, rarely more than a few months. But if these animals are fed bile and liver, they continue to live almost the normal course of life. Even a small amount of bile causes marked improvement of the animal's condition. It is evident that bile is necessary for life of man and experimental animals. Under experimental conditions, Schwann, in 1844, was the first to investigate the effect of biliary fistula. All of his dogs with complete external fistula died of emaciation and general loss of weight; 1 dog lived 80 days. He concluded that bile is essential to life, and even today there is no satisfactory evidence to contradict his statement. Life may continue for a few months; but when there is a complete biliary fistula, there is a definite progressive downward trend to an inevitable death within a few months. The average length of life of 34 cases was 7 months, and the maximum was 3 years. The principal disturbance was anemia (Balfour).

One dog was kept alive for 8 weeks on a meat diet by Bidder and Schmidt in 1852. Since then, fistula bile from a great variety of animals, such as dog, cat, pig, sheep, guinea-pig, horse, rabbit, and man, has been studied. Biliary fistula frequently followed operations on the gallbladder where only cholecystotomies were done. A review of the effect on man of loss of bile has been made recently by Wangensteen, who points out that life goes on fairly well for months, and even for years, by refeeding with bile. Judd and White found no ill effects from prolonged external drainage of the bile provided the bile was restored to the intestinal tract.

A woman was operated on in 1890 for complete obstruction of the bile duct by Paton, resulting in a complete biliary fistula. The bile was caught in a caoutchouc bag. She appeared to be in excellent health 2 years later, with weight normal and bowels normal. A chemical and physical examination of the bile was normal. Nothing was said about the character of the stool; so one questions the possibility of the bile fistula being only partial.

In view of recent discoveries of the enterohepatic circulation of the bile salts and vitamins, bile must be considered as a very composite liquid, containing excretory and secretory substances, which are essential.

ANEMIA

Continued external biliary fistula is always marked by a profound progressive anemia, diminution of hemoglobin and red blood cells. Part of the anemia is due to the inability of the intestine to absorb food properly; part, to bleeding into the tissues; and part, to bleeding from mucous surfaces. There is an excess bile-pigment production which is about seven times the normal output (Queen, Hawkins, and Whipple), which would indicate the appearance of petechiae with the formation of pigment from hemoglobin.

A fistula was made in dogs by Seyderhelm and Tammann (1752) between the gallbladder and the urinary bladder, and the common duct was ligated. In 1 month the dogs lost 40 per cent of their weight; hemoglobin went down; the red blood cells likewise decreased; but the leukocytes increased. The progressive loss of blood was the same whether the spleen was removed before or after the bile fistula was made. Death occurred sooner in dogs with splenectomy (Queen, Hawkins, and Whipple). The fistula dogs which were fed 50 cc. of ox gall twice daily did not have such a progressive anemia. The exact constituent in the bile which prevented anemia is unknown.

OSTEOPOROSIS

Osteoporosis in dogs was first definitely shown, by Pavlov in 1904, to be the result of exclusion of bile from the intestinal tract. A few weeks following the making of the fistula, spontaneous fractures occurred. (Clinical records show that many persons with long-continued external biliary fistulas have spontaneous fractures.) Osteoporosis or rickets developed because of loss of calcium, deficient sunlight, and lack of vitamin D. The age determined whether rickets or osteoporosis developed, as rickets occurred only in the young. Rabl (1532) verified this with rats. Osteoporosis developed when there was bile fistula, causing a chronic loss of alkali with resulting acidosis. Dieterich (458) observed an enlargement of the parathyroids and osteoporosis, owing to a persisting biliary fistula.

Further investigations in bile fistula dogs have shown definite alterations in the bone calcium. The compact bone became porous, and there was an excess deposit of calcium at the epiphyseal line. This has been shown by chemical investigations of the bones and by Roentgen-ray and pathologic examinations. Dogs with fistula between the gallbladder and urinary bladder were used by Tammann (1877) and Pagliani. Blood calcium was followed; and even though the dog declined much in weight, the blood calcium remained normal; fractures occurred spontaneously in the ribs of many of the dogs. Roentgen-ray examinations, taken at different intervals, showed progressive decalcification of the bones. Bone regeneration following rib resection at the end of 5 months was negative; while that of the controls, done at the same time, was normal as to quantity and quality. Activated cholesterol, given subcutaneously, and sunlight prevented demineralization and promoted healing.

Five patients with complete external biliary fistula were observed by Düttmann. He found an acidosis with a fall in the alkali reserve. The loss of calcium in the bile was made up by mobilization of calcium, presumably from the bones,

the blood calcium remaining normal. The loss of calcium and the lack of vitamin D from disturbed fat ingestion caused a porotic malacia. Vitamin administration did not prevent bone changes so long as the acidosis remained. The patients with total external biliary fistulas were studied after fasting for 24 hours. The urine phosphates, primary and secondary, had increased in quantity; the serum calcium was increased to 12.4 per cent; the alkali reserve (blood) Van Slyke was 39.5 cc. minimum to 50.4 cc. maximum; the calcium of the urine was increased; the volume of the urine excretion was twice that of the bile excretion (urine 1,000 cc. to bile 500 cc.). The continuous loss of bile alkali caused protracted acidosis; the acid excretion in the urine increased, and the alkali reserve in the blood decreased below normal; the calcium of the blood increased mobilization from the depots, and the calcium loss in the bile continued high. The more alkali there was in the bile, the more acid there was in the urine; pH of the bile increased, and that of the urine decreased after administration of sodium bicarbonate by mouth. Bile fistula caused acidosis, which served to alter the calcium metabolism. This altering of the acid condition of the body resulted in mobilization of calcium from the depots, namely, the skeleton. The absence of bile from the intestine influenced the fat digestion, so that a smaller quantity of vitamins A and D was absorbed. The calcium loss through acidosis and the vitamin deficiency caused a *porotischen Malacie* (osteomalacia). Vitamins alone will not prevent the alteration of the bone from taking place. The feeding of bile and absorption of vitamins caused a normal calcium metabolism through an increase of the acid in the blood. Foster, Hooper, and Whipple (617, 618) have reported the development of abnormalities in the bones of dogs with prolonged external biliary fistula. The feeding of bile salts is not as effective as whole bile. But bile salts and vitamin D by mouth are sufficient to produce a calcium-phosphorus balance and to cure the osteoporosis in rats and dogs (Greaves and Schmidt). Bile salts play an important role in

the absorption of calcium from the intestine. Milk and bile salts cause an increase in calcium in the blood (von Beznák).

Osteomalacia may be due to inability to absorb vitamins because of the absence of bile from the intestine or the failure of the enterohepatic circulation of bile salts associated with the vitamin preservation or intake. More likely, the absence of bile from the intestinal tract prevents the absorption of fats which contain the fat-soluble vitamin, and that, in turn, modifies calcium and phosphorus metabolism.

Vitamin A can be absorbed from the intestine in the absence of bile, but bile is essential for the absorption of carotin in rats. In obstructive jaundice and phosphorus poisoning the ability of the animal to convert carotin into vitamin A is reduced. Bile acids are necessary aids in carrying carotin across the intestinal mucosa. Fats are not necessary (Greaves and Schmidt). The feeding of vitamin A and cholic acid (gallosterin) prevents rickets in rats when the diet contains normal portions of phosphorus and calcium (Murao). A similar effect is produced in rats when methyl-ester- β -cholic acid which has been treated with ultraviolet rays is fed; the rachitic bones return to normal (Kikuzawa). Viosterol (vitamin D, irradiated ergosterol), given daily to dogs, has no effect on the calcium output in bile, or on serum calcium, which usually runs slightly lower than the bile calcium (Jones). Bile given to chicks does not enhance the antirachitic action of vitamin D. Bile contains very little vitamin D. Bile acids aid in the resorption of vitamin C (Klodt). Synthetic crystalline vitamin D has an antirachitic effect (Windaus). Fat-soluble vitamin deficiency causes a decreased pH and lessened buffer action in rabbits—changes parallel with avitaminosis (Usuki). The bile acids have no effect on the blood-calcium content when the vagi have been sectioned. The bile acids act on the vagi antagonistically to the sympathetic nervous system and opposite to the action of adrenalin (Sekitoo). The decrease in calcium in the blood, urine, and feces can be brought to normal and the calcium-

phosphorus balance maintained in rabbits by feeding bile salts (Sekitoo, Okii). There is still another possible action of bile acid: the inhibiting action of the amino acids on lipase is decreased, and bile acid then works on the fat-splitting in the gut, preparatory to absorption (Karasawa).

The blood phosphatase is present in the bile in a considerable amount (King). With obstruction of the common duct the serum phosphatase is increased thirty to one hundred times the original value within 6 days. But according to Uraki, bile acids inhibit phosphatase action in rabbits and increase phosphatase action. The synthesis of glycerophosphoric acid is increased by cholic acid (Takata). The increase of inorganic and organic phosphoric acid in the blood, caused by cholic acid, is only temporary and is followed by a decrease below normal after 2-3 hours (Kimura). This interrelation of bile acid, vitamins, and bone metabolism is rather heterogenous and necessitates much more extensive work before the effect of bile on osteomalacia and rickets can be explained.

RÉSUMÉ

External biliary fistula should always be avoided in man if it is possible to make a gastrobiliary or enterobiliary fistula. If this is impossible, the next operation, of choice, is external biliary fistula, as contrasted with complete obstructive jaundice. The length of life in obstructive jaundice is always limited. In simple external biliary fistula, proper supplementary feedings of bile and liver can always be accomplished, and thus life may be prolonged for an unknown period.

Bile loss seems to be far afield from the toxicity of bile. The toxicity is due to the absence of bile, not to its presence.

CHAPTER XXVI

THERAPEUTIC EFFECTS OF BILE ACIDS

THE retention of bile in the body causes certain toxic symptoms, and the failure of bile to reach the intestine prevents proper digestion and results ultimately in death. The retention of purely excretory bile constituents in the blood stream inhibits the normal cellular activity. It is necessary for life that the metabolic products be ultimately and properly removed, and that bile aid in the absorption of food from the intestine. A substance which would cause these functions to be performed satisfactorily has long been sought. Various substances have been used empirically during the past three thousand years. Some of these substances have been classed as cholagogues. Strictly speaking, a cholagogue is a substance which causes the expulsion of bile from the biliary tract. The most desirable substance, a choleric, would cause actual secretion and excretion of bile constituents. The only really effective stimulant of bile formation is bile or bile salts. The ordinary bile acids are too toxic for use in sufficient quantities, either by mouth or intravenously. When injected, they act deleteriously on the blood, heart, and various body tissues. The choleric effect has been shown by Neubauer and also by Pohl. Some of the bile acids do not stimulate the secretion. The most satisfactory are apocholic, desoxycholic, dehydrodesoxycholic, oxycholic, and dehydrocholic acids. A choleric is desired which is effective, yet relatively nontoxic.

DEHYDROCHOLIC ACID

Dehydrocholic acid was first synthesized by Hammarsten, in 1881, by oxidizing cholic acid with chromtrioxide. It is not a natural bile constituent. The structural formula was deter-

mined by Wieland in 1929. Dehydrocholic acid is changed to sodium dehydrocholate by the addition of sodium hydroxide. This latter form is used for injection. It is discussed here because of the important use made of bile acids to stimulate the secretion of bile and the possible toxic effects it might have on the recipient. It is used intravenously or orally. The toxic action of bile acids has been shown in previous sections. The various bile acids have different relative toxicities, for example, desoxycholic acid, which is very toxic when compared with dehydrocholic acid. The toxicity of the bile acids depends on their surface activity, for the lower the surface tension the greater the toxicity. The surface activity is related not to the choleric effect but to toxicity. Dehydrocholic acid is one of the least surface-active of the bile acids, and for this reason its toxicity was investigated.

ACTION ON BLOOD

Hemolysis of rabbit and human corpuscles in saline solution was caused by 0.63 per cent sodium dehydrocholate, while only 0.04 per cent sodium desoxycholate was required, according to Neubauer (1367). The concentration of sodium dehydrocholate necessary to produce hemolysis in vitro was much greater than that ever reached in vivo with the ordinary therapeutic intravenous injection. It has also been found that, if the dehydrocholate was injected into blood serum, the serum afforded additional protection. Regan and Horrall, using human corpuscles in physiologic saline solution, found that sodium dehydrocholate, in comparison with some very pure sodium glycocholate, had a very slight hemolytic effect. There was a decrease in the bilirubin content of the blood in patients a short time after intravenous injection of 2 gm. of sodium dehydrocholate (Adlersberg and Neubauer [21]); a few hours later there was an increase; and 24 hours later, a second decrease. The cholesterol content of the blood serum was considerably lessened by intravenous injection of sodium dehydrocholate; yet in one case it rose

higher (Gardner and Gainsborough). The resistance of the red blood corpuscles was lessened. The cholesterol content of the red blood corpuscles was lessened after long-continued administration of sodium dehydrocholate to animals, but later rose higher than the original value. This later rise caused a greater resistance of the red blood cells and also an increase of the protecting power of the serum against the action of bile acids.

ACTION ON BACTERIA

Dehydrocholic acid in small concentrations inhibits the growth of both *S. aureus* and pneumococcus (Kaufteil and Neubauer [978]). It has no effect on *B. typhosus* or *B. coli* in a 3 per cent solution. The possibility has been suggested that sodium dehydrocholate may have a bactericidal action in cases of inflammation of the gall passages. Ziegler (2172) has shown that sodium dehydrocholate is one hundred and twenty times less hemolytic for human blood cells than sodium taurocholate or sodium glycocholate but that it dissolves pneumococci in the same time and in the same dilute concentration as the other bile salts.

ACTION ON THE HEART

Sodium dehydrocholate, in concentrations varying from 1:800 to 1:200, has no effect on the isolated frog heart, according to Neubauer (1367). Two per cent solution of sodium dehydrocholate stops the heart in 10 minutes, whereas 1:1800 concentration of sodium desoxycholate stops the heart after 1 minute. He concluded that desoxycholate is twenty-five times more toxic to the heart than sodium dehydrocholate.

Weak concentrations of sodium dehydrocholate (40 mg. per kilogram) increased the irritability of the vagal endings or junctions in dogs, cats, and rabbits under barbital or chloralose anesthesia, according to Ries and Still (1575). The same amounts decreased the sensitivity of the vasoconstrictor endings or junctions. In the experiments with intact vagi no significant changes were detected in the pulse following the

injection of bile salts (including sodium dehydrocholate), because of the diminution or absence of vagus tone in anesthetized animals.

Sodium dehydrocholate² has less effect on the blood pressure than sodium glycocholate, as found by Regan and Horrall, who worked on barbitalized dogs. The fall in pressure following intravenous injections of sodium glycocholate is about twice as great and much more sudden than that following injections of sodium dehydrocholate. The limits of fall of blood pressure are from 4 to 80 mm. of mercury for sodium dehydrocholate and from 24 to 104 mm. for sodium glycocholate.

Six patients showed no change in blood pressure; while 12 patients, who had some degree of hypertension, showed a decrease in blood pressure from 12 to 30 mm. of mercury, following the intravenous administration of sodium dehydrocholate by Adlersberg and Taubenhaus.

ACTION ON RESPIRATION

There was no change in the average respiratory rate of 19 dogs following injection of 2 gm. of sodium dehydrocholate. With similar amounts of sodium glycocholate there was an average decrease in respiratory rate of 18.70. Eight dogs showed a decrease, whereas 3 dogs showed no change. When rabbits were injected with large doses of sodium dehydrocholate, they became dyspneic; and necropsy showed bronchopneumonic patches in the lung and pleural hemorrhage. The respiration rate in dogs and rabbits was not affected by the intravenous injection of small doses of sodium dehydrocholate (Regan and Horrall).

EFFECT ON THE OUTPUT OF BILE

Dog bile was collected at 15-minute intervals by means of a cannula in the common duct with the cystic duct ligated. The dogs were under barbital anesthesia (Regan and Hor-

² Dehydrocholic acid and its sodium salt, decholin sodium, were prepared and supplied by Riedel-De Haen.

rall). Control periods were run first for at least 1 hour. Two grams of sodium dehydrocholate were then injected intravenously. The average increase in bile flow was ten times the basal for $2\frac{1}{2}$ hours following the injection in 7 dogs. The bile began to flow faster within 1 minute after injection. The length of time required for the bile flow to return to normal was from 2 to 5 hours, the average being $3\frac{1}{2}$ hours. In 6 dogs the bile changed from a dark greenish-brown to a clear-amber color. In one the color changed to a clear red, resembling hemolyzed blood. Total solid determinations were run on these samples. There was a marked decrease in solids, becoming more marked in later samples. Bile-pressure determinations were made on 7 dogs by connecting a cannula in the common duct with a bromoform manometer. The cystic duct was ligated. The bile was allowed to reach its maximum secretion pressure, and then 10 cc. of 20 per cent sodium dehydrocholate was slowly injected intravenously at body temperature. The average normal bile pressure was found to be 341 mm. of water. As a result of the injections the average pressure rose to 385 mm. of water, or a 13 per cent increase (1548).

Dehydrocholic acid, according to Neubauer, causes a two-fold to fivefold increase in bile secretion following intravenous injection in rabbits and in patients with biliary fistulas.

The use of sodium dehydrocholate as a choleretic was investigated by Wakefield, Powelson, and McVicar on 20 patients divided into three groups: one group in which external biliary drainage had been established by placing in the common bile duct a T-tube leading to the outside; a second group in which the gallbladder opened to the outside, the bile duct being completely occluded by pancreatic neoplasm; a third group where normal bile was obtained with duodenal bucket and tube. The experiments were usually begun 2 hours after the noon meal. The bile was allowed to flow for 1 hour as a control period, before the actual experiment began. Two grams of decholin, dissolved in 100 cc. of 10 per cent glucose,

were injected within a period of 5 minutes. There was an increase in bile flow within 15 minutes, and sometimes more quickly. The increase in flow usually ceased within an hour. At periods of maximum activity the color of the bile was less intense than the normal. Bile salts, bilirubin, and cholesterol were decreased relatively and absolutely. There was an increase in bile flow in 18 of the 20 cases. The drug was given to two subjects in whom the bile flow was not free: in both, the concentration of bilirubin rose rapidly; one had a stone in the common duct, and the injection was followed by pain in the region of the liver.

The volume of bile secreted was more than doubled following the intravenous injection of sodium dehydrocholate into rabbits (Adlersberg and Neubauer [22]). Parallel with the rise of bile volume, the surface tension decreased; but later it increased. There was a relative and an absolute decrease in the bilirubin content of the bile after injection of dehydrocholic acid.

Sodium dehydrocholate is excreted by the liver up to 95 per cent of the amount injected, according to the experimental work of Adler and Schmidt.

ACTION ON THE LIVER

Parenchymatous degeneration of liver cells and collections of round cells in the interlobular spaces were found at necropsy of rabbits which had been given a lethal dose of sodium dehydrocholate by Gillert. There was also an increase in hemosiderin in the spleen.

Small doses of sodium dehydrocholate given intravenously to rabbits were ineffective, but not harmful to liver cells; but doses of 0.25 gm. per kilogram of weight caused destruction of the hepatic cells, as found by Bratianu, Solomon, and Bratianu. The effect on the liver of the injection of bile salts in cats with total bile stasis was shown by Cantarow and Stewart. The plain stasis showed focal midzonal necrosis; the treated, "moth-eaten" areas of degeneration. In plain stasis

there was less widespread hepatic parenchymal damage, regeneration was less marked, proliferation of the small bile ducts greater, and there was a greater increase of connective tissue.

ACTION ON THE KIDNEYS

A rapid and decided decrease in the bilirubin content of the urine of patients following injection of 2 gm. of sodium dehydrocholate intravenously was reported by Adlersberg and Neubauer (21). There was, however, a marked diuresis. Passive congestion of the kidney, with fat in the tubules, following injection of lethal doses of sodium dehydrocholate into rabbits, has been observed by Gillert. There was, following intravenous or peroral application of sodium dehydrocholate, as a rule, a fall in the surface-tension curve of the urine in normal individuals—a decrease or fall which was not present in patients suffering from severe liver disease (Adlersberg [13]). The diuretic action of sodium dehydrocholate seems to have been frequently observed in experimental animals and in man following intravenous use.

TOXIC EFFECTS ON ANIMALS

In tests on 36 frogs with sodium dehydrocholate (0.2–5.0 mM per kilogram) and 14 frogs with sodium choleate the former proved to be about one-fifth as toxic as the latter, according to Regan and Horrall.

Large doses of sodium dehydrocholate were injected subcutaneously into guinea-pigs by Neubauer (1367): 4.4 gm. per kilogram of body weight caused death in 6 hours, whereas from 0.5 to 0.6 gm. per kilogram of cholic and desoxycholic acid caused death in the same length of time.

The lethal dose of bile salts for rabbits was determined by Gillert, who reported the dosage of sodium dehydrocholate to be between ten and eleven times greater than that of sodium glycocholate and sodium taurocholate. The symptoms of the lethal dose were diarrhea, disturbance of circulation and breathing, mydriasis, clonic and tonic convulsions, increased

peristalsis and dyspnea, uterine contractions and abortion in pregnant animals, and stiffening immediately after death. The pathologic findings in the liver were parenchymatous degeneration of liver cells, fatty degeneration of Kupfer cells, and collection of round cells in the interlobular spaces; in the spleen, an increase in hemosiderin; in the kidney, passive congestion and fat deposits in tubules; in the heart, fine drops of fat deposit in muscle; in the lungs, bronchopneumonic patches and pleural hemorrhage; in the lymph nodes, swelling of lymph follicles and swelling of nuclear centers in Peyer's patches. There was hemorrhage in the peritoneum; hemorrhage in the capsule of thymus; hemorrhagic erosions of stomach and gut; death was due to systolic or diastolic standstill. The microscopic sections showed that the bile salts were blood and other tissue poisons. Bile salts poisoned the central nervous system, as shown by dyspneic breathing and convulsions.

A rabbit weighing 3,800 gm., given daily subcutaneous injections of 0.5 gm. of sodium dehydrocholate for 48 days by Gardner and Gainsborough, lost 800 gm. in weight during this time. The dose was increased to 0.8 gm., and the animal died on the twenty-ninth day of administration of the larger dosage, having lost an additional 300 gm. in weight. No definite cause for death was found at post-mortem examination. Macroscopic examination of the tissues and organs revealed no changes. The urine was tested several times for albumin and hemoglobin, with negative results.

Intravenous injection of a 20 per cent solution of sodium dehydrocholate into 7 dogs caused defecation, vomiting and hyperexcitability. Deaths were observed following doses ranging from 0.024 to 0.72 gm. per kilogram of body weight (Regan and Horrall). Similar reactions were produced by sodium glycocholate in much smaller doses. Hypodermic injections of sodium dehydrocholate in concentrations up to 20 per cent did not induce local necrosis, as did sodium glycocholate. One dog, weighing 8.8 kg., was injected intravenous-

ly by Neubauer (1367), on succeeding days, with 0.6, 1.55, and 3.8 gm. of sodium dehydrocholate; also with a 6-32 per cent solution in quantities ranging from 0.0682 to 0.43 gm. per kilogram. There was no retardation of pulse and no hemoglobinuria. Following injection of 0.51 gm. per kilogram intravenously a week later, the dog vomited and had diarrhea. It recovered within a few hours.

The respiratory quotient and basal metabolism of white rats was determined by Hokan following the intraperitoneal injection of sodium dehydrocholate. There was a 12 per cent increase over the normal on injection of doses which were equivalent to the human dosage of 0.006-0.012 gm., 1 hour before making the determination. Larger doses caused diarrhea.

Sodium dehydrocholate, 2 gm., was injected intravenously three times daily into patients by Neubauer. He noticed no harmful symptoms; there was no marked change in pulse, although there was often a slight decrease or a slight increase. The patients complained of a bitter taste during the injection. No toxic effects were observed by Adlersberg (13) in patients following an injection of 2.5 gm. of sodium dehydrocholate intravenously or the oral administration of 4 gm. No apparent harmful effects followed similar administration even to patients with jaundice.

Sodium dehydrocholate was used by Adlersberg and Neubauer in 30 cases of febrile conditions of the liver and bile system, the febrile condition being very pronounced in 7 patients. Administration was usually intravenous, the dose being 2 gm. of a 20 per cent solution. A bitter taste was experienced at once, and they felt as though something were going on in the liver. The fever was quickly reduced; pain was materially diminished; and recovery was rapid and maintained. Administration in some cases was repeated for several days. If, on injection, some of the sodium dehydrocholate got into the tissues surrounding the vein, it produced no harmful effects. No toxic effects were observed by Wakefield, Powel-

son, and McVicar on administration of 2 gm. of sodium dehydrocholate intravenously to 20 patients. Sodium dehydrocholate was used by Engler, in the treatment of 230 cases of bile-passage disease, without any harmful effects. In some cases, following the administration of sodium dehydrocholate for the first few times, there was increased pain in the gall-bladder region and bloody stools. These symptoms vanished in a few days, however, and did not return, although the injections of bile salts were repeated. Movements of the stomach were seen in patients by Unverricht and Freude, by means of Roentgen rays. Administration of sodium dehydrocholate increased tonus and excited peristalsis.

Arthritis frequently decreases with onset of jaundice; so bile salts have been given in a number of cases, with more or less favorable results. The relief from pain is very gradual; hence not spectacular. Intravenous sodium dehydrocholate acts more rapidly, especially when very large doses are given (Horrall). The inactivating effect of jaundice in chronic infectious arthritis and fibrositis has not been explained by Hench.

Arsphenamine poisoning is rapidly relieved by intravenous sodium dehydrocholate. The arsenic is excreted in the urine more rapidly, and the hepatitis recedes (Appel).

Migraine in 22 patients was treated with sodium glycocholate capsules, 2-20 gr. three times a day; 19 patients improved (Hunt). This work could not be confirmed by Horrall. The sudden disappearance of pain in this type of case makes the interpretation of the results hazardous.

RÉSUMÉ

Sodium dehydrocholate is toxic only when used in excessive amounts intravenously or orally. The margin between the therapeutic and toxic action is so great that a wide safety zone furnishes a much-needed factor in treatment.

Sodium dehydrocholate is an active choleric and chologogue.

CHAPTER XXVII

GENERAL CONCLUSIONS

IN OUR present state of knowledge concerning the presence of bile in the blood stream and tissues we are hardly justified in assuming that the cause of the symptoms of jaundice are due to bile per se. It has long been assumed that, because the patient is jaundiced (yellow), the symptoms are directly due to the bile. Thus, to the pigment itself has been ascribed the toxicity. No parallel studies have been made to show the relationship of the quantity of bile pigment to the quantity of the bile salts in the tissues other than in the blood serum. Up to the present time there has been no method of determining bile salts accurately in such small quantities as they may occur in the normal blood stream. Recently, a modified method of the Pettenkofer reaction has been developed, but there is also a reaction with ions other than those of the toxic cholate portion of bile salts. There are many forms in which bile salts may appear in the human bile.

The van den Bergh reaction tells only how much bilirubin is present. But since the recent experimental work has proved that bilirubin is nontoxic, it is evident that the van den Bergh reaction does not test for the substance which causes the symptoms. Since there is a known failure of relationship of the quantities of bilirubin to bile salts, such a test cannot be of much use. As an indicator of the degree of jaundice pigmentation, it is satisfactory. But it does not tell whether there is an overproduction of pigment or a faulty elimination; nor does it determine the location of the lesion: whether it is in the larger bile ducts, in the liver, or elsewhere. Bilirubin is produced in tissues other than the liver; and since it appears so abundantly in the bile, probably because the bile is alkaline and keeps it in solution, as bilirubin

is most soluble in alkaline solutions, or the portal of exit is extremely low in the liver, conclusions cannot be drawn that bile salts are likewise retained.

There is no satisfactory evidence as to where all the bile salts are formed. It may be that, when a quantitative method has been developed for bile salts to such a degree of accuracy as that for bile pigment by Sheard, it will be possible to locate the site of their formation.

In obstructive jaundice there is a large variety of possibilities, namely, actual injury by the bile salts to the various tissues of the body, such as has been repeatedly demonstrated by the injection of bile salts by various means in experimental work; impairment of intestinal digestion by the absence of the bile from the intestinal tract; and the absence of its inhibiting action on the intestinal flora, thereby permitting bacteria to manufacture toxic substances which may be absorbed from the intestine.

Progress in the investigation of jaundice has been seriously impaired, if not stopped, by the failure to discover an accurate specific quantitative test for bile salts. A test for very minute quantities is essential. The complexity of the bile salts, the various combinations of cholate, with other substances, and the probable numerous physical or loose combinations will impede progress.

Substances, other than bile salts, which have been toxic are found in the bile; but many of these either have been detoxified by the liver or occur in infinitesimally small amounts and are thus relatively nontoxic. Other substances are actually rendered nonpoisonous by the bile itself.

The very fact that experimental research on bile is in progress in almost every civilized country in the world is evidence of the widespread interest in this question. The occurrence of jaundice in its multifarious forms throughout the ages, and its world-wide presence in various degrees, as found by close observers, makes its investigation exceedingly important.

The relation of the liver to the output of bile involves an extremely complicated process. No attempt has been made in this monograph to elucidate the other numerous activities of the liver or to incorporate here, in a statement, the other relations of the liver to disease.

It has been the aim of the writer to point out the toxic action of bile, and more particularly to show that it is the bile salts that are responsible for this toxic action; that bile pigment is not toxic and that the discoloration caused by the pigment, namely, jaundice, is a symptom and not a disease; and that a great number of symptoms that have been attributed to bile are a part of a syndrome and not directly attributable to the action of bile itself. No attempt has been made to discuss all the diseases in which jaundice occurs as a symptom, but only those in which the toxic action of bile may have an influence.

The primary purpose of this book has been to state and correlate experimental work that has been done, and to point out the great need for further experimental investigation and clinical observation.

BIBLIOGRAPHY

This extensive but selective bibliography has been included for reference to scientific literature. Most of the dissertations and theses are available in the Surgeon General's Library. Original titles have been used except in Slavic and oriental languages, in which instances translations have been used and appear in brackets.

Items marked with an asterisk (*) have an extensive bibliography.

1. ABDERHALDEN, E. Notiz zum Gallenfarbstoffnachweis in Körperflüssigkeiten, Geweben und Gallensteinen. *Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs.*, 4:883, 1909.
2. ABRAMI, P. Le Purpura des hépatiques. *Ann. de med.*, 37:71-79, 1935.
3. ARCHARD, C.; BOUTARIC, A.; and BERTHIER, P. Recherches sur la viscosité des solutions de bile. *Compt. rend. Acad. d. sc.*, 14:1049-51, 1937.
4. ADELL, G. Untersuchung über das Vorkommen von Cholsäure im Blute bei Psychosen. *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 155: 749-57, 1936.
5. ADLER, A. Klinische Methode der (approximativ-) quantitativen Urobilinbestimmung in den Ausscheidungen des Körpers. *Deutsches Arch. f. klin. Med.*, 138:309-20, 1922.
6. ADLER, A. Über Verhalten und Wirkung von Gallensäuren im Organismus. *Ztschr. f. d. ges. exper. Med.*, 46:371-424, 1925.
7. ADLER, A. Die Leber als Excretionsorgan. *Handbuch der Normalen und Pathologischen Physiologie*, 4:769-801, 1929.
8. ADLER, A., and BREHM, W. Gallenstudien. Methode der dauerenden Gewinnung absolut steriler Gesamtgalle bei Hunden. *Ztschr. f. d. ges. exper. Med.*, 48:148-53, 1925.
9. ADLER, A., and SCHMIDT, E. Diagnostische und therapeutische Verwendbarkeit der Gallensäuren und des Tetrachlorphenolphthaleins bei Erkrankungen der Leber und Gallenwege. *Fortschr. d. Ther.*, 1: 733-42, 772-76, 807-14, 1925; *Deutsche med. Wchnschr.*, 52:301, 1926.

10. ADLER, A.; SOLT, J.; and HERMER, J. Über Verhalten und Wirkung von Gallensäuren im Organismus. *Deutsche med. Wchnschr.*, 51: 1689, 1925.
11. ADLER, E. Über die Einwirkung von Gallensäuren auf die Lösung von Kalkseifen im Stuhl. *Arch. f. Verdauungskr.*, 40: 174-83, 1927.
12. ADLER, E., and STRAUSS, L. Beitrag zum Mechanismus der Bilirubinreaktion im Blutserum. *Ztschr. f. d. ges. exper. Med.*, 44: 1, 1924.
13. ADLERSBERG, D. Über die Ausscheidung oberflächenaktiver Stoffe im Harn Normaler und Leberkranker. *Ztschr. f. d. ges. exper. Med.*, 42: 194-212, 1924.
14. ADLERSBERG, D. Über die Oberflächenspannung von Körperflüssigkeiten bei normalen und pathologischen Zuständen. *Wien. klin. Wchnschr.*, 38: 1051-55, 1925.
15. *ADLERSBERG, D. Gallensekretion und Gallenentleerung. *Klinisch-experimentelle Untersuchungen*. Leipzig and Wien: Franz Deuticke, Verlags. Nr. 3306, 1929.
16. ADLERSBERG, D. Zur Rolle der Leber im Wasserhaushalt. *Wien. Arch. f. inn. Med.*, 25: 401-62, 1934.
17. ADLERSBERG, D., and LUSTIG, B. Zur Pharmakologie der Apocholsäure und der Dehydroapocholsäure. *Arch. f. exper. Path. u. Pharmakol.*, 181: 610-16, 1936.
18. ADLERSBERG, D., and NEUBAUER, E. Über die therapeutische Verwendung der Dehydrocholsäure. *Wien. med. Wchnschr.*, 33: 1716-18, 1924.
19. ADLERSBERG, D., and NEUBAUER, E. Dehydrocholsäure als Mittel zur Behandlung der Cholecystitis und Cholangitis. *Klin. Wchnschr.*, 4: 310, 1925.
20. ADLERSBERG, D., and NEUBAUER, E. Über die therapeutische Verwendung der Dehydrocholsäure bei fieberhaften Erkrankungen der Gallenwege. *Wien. Arch. f. inn. Med.*, 10: 59-70, 1925.
21. ADLERSBERG, D., and NEUBAUER, E. Über die Beeinflussung von Galle, Blut und Harn durch Zufuhr von Dehydrocholsäure. *Ztschr. f. d. ges. exper. Med.*, 48: 291-305, 1926.
22. ADLERSBERG, D., and NEUBAUER, E. Zur Ausscheidungsfunktion der Leber. *Arch. f. exper. Path. u. Pharmakol.*, 117: 147-68, 1926.
23. ADLERSBERG, D., and PORGES, O. Über den Nachweis von Bilirubin und Urobilin in den Faeces mit Trichloressigsäure. *Biochem. Ztschr.*, 150: 348, 1924.
24. ADLERSBERG, D., and TAUBENHAUS, M. Blutdruck, Blutcholesterin und Diurese nach Zufuhr von Gallensäuren. *Biochem. Ztschr.*, 177: 400-405, 1926.
25. AESCHYLUS. (1) Agamemnon 1660; (2) Choëphoroe 182. Opera. C. J. Blomfield (ed.). London, 1834-39.

26. AFANASSIEW, M. Über Icterus und Hämoglobinurie, hervorgerufen durch Toluylendiamin und andere Blutkörperchen zerstörende Agentien. *Ztschr. f. klin. Med.*, 6:281-331, 1883.
27. AGRIFOGLIO, M., and CANAVERO, M. Riserva alcalina, calcio, grassi dopo derivazione complete della bile. *Arch. ital. di chir.*, 37:594-618, 1934.
28. AIZAWA, Y. Studies in experimental scurvy. On the amount of bile secreted, and its bile salts and cholesterol contents in guinea pigs fed on a vitamin C free diet. *J. Biochem.*, 21:487-504, 1935.
29. ALBERS, J. F. H. Über die Wirkung der Glycocholsäure auf Muskel- und Nerven-thätigkeit. *Virchows Arch. f. path. Anat.*, 23:582-87, 1862.
30. ALBERTONI, P. La Sécrétion biliaire dans l'inanition. *Arch. ital. de biol.*, 20:127-33, 134-38, 1893.
31. ALBOT, GUY. Hépatites et cirrhoses. Masson et Cie, 1932. Pp. 248.
32. ALBU, A. Zur Physiologie und Pathologie der Gallensecretion. *Berlin Med. Ges. Verh.* (1900), 2:218-38, 1901; *Klin. Wchnschr.*, 37:866-69, 891-94, 1900.
33. ALDRICH, M., and BLEDSOE, M. A quantitative Pettenkofer test applicable to the determination of bile acids in the blood. *J. Biol. Chem.*, 77:519-37, 1928.
34. ALLODI, A., and QUAGLIA, F. Sul contenuto in sali biliari della bile in condizioni normali e patologiche. *Gior. d. r. Accad. di med. di Torino*, 96:145-55, 1933.
35. ALLODI, A., and QUAGLIA, F. Il Solfo della bile. *Gior. d. r. Accad. di med. di Torino*, 96:168-78, 1933.
36. ALVAREZ, W. C. Differences in the action of drugs on different parts of the bowel. *J. Pharmacol. & Exper. Therap.*, 12:171-91, 1918.
37. ALVAREZ, W. C. The influence of drugs on intestinal rhythmicity. *Am. J. Physiol.*, 46:554-62, 1918.
38. ALVAREZ, W. C. The mechanics of the digestive tract. New York: Paul B. Hoeber, 1922.
39. ALVAREZ, WALTER C. Intestinal autointoxication. *Physiol. Rev.*, 4:352-93, 1924.
40. AMANTEA, F. Osservazioni bacteriologiche sulla bile umana, con particolare riguardo allo streptococco. *Policlin.*, 41:243-47, 1934.
41. AMOROSI, O. Le Alterazioni degli organi conseguenti alla derivazione totale della bile dall'intestino. (Nota preventiva.) *Gior. di clin. med.*, 13:1127-30, 1932.
42. AMOROSI, O. Le Alterazioni degli organi, conseguenti alla derivazione totale della bile dall'intestino. *Ann. ital. di chir.*, 12:1-40, 1933.

43. AMOSS, H. L., and POSTON, M. A. Cultivation of *Brucella* from stools and bile; further observations. *J.A.M.A.*, 95:482-83, 1930.
44. ANDERSON, A. P., and HART, P. D'A. The lysis of pneumococci by sodium desoxycholate. Effect of varying concentrations of sodium chloride. *Lancet*, 2:359-60, 1934.
45. ANDREWS, E. Liver autolysis in vivo. *Proc. Soc. Exper. Biol. & Med.*, 27:987, 1930.
46. ANDREWS, E. The etiology of gall stones. Read before Chicago Surgical Society, Nov. 6, 1931.
47. ANDREWS, E. Analysis of duct bile from diseased livers. *Arch. Surg.*, 25:1081-89, 1932.
48. ANDREWS, E. Acholic cachexia. *Proc. Inst. Med.*, Chicago, 10:211, 1935.
49. ANDREWS, E., and ARONSOHN, H. G. Possible chemical cholecystitis. *Proc. Inst. Med.*, Chicago, 11:140, 1936.
50. ANDREWS, E., and ARONSOHN, H. G. Relative toxicity of different bile salts on the normal gallbladder. *Proc. Soc. Exper. Biol. & Med.*, 34:765-67, 1936.
51. ANDREWS, E.; DOSTAL, L.; GOFF, M.; and HRDINA, L. The mechanism of cholesterol gall-stone formation. *Ann. Surg.*, 96:615-24, 1932.
52. ANDREWS, E.; HARKINS, H. N.; HARMON, P. H.; and HUDSON, J. Shock syndrome following subcutaneous injection of bile or bile salts. *Ann. Surg.*, 105:392-400, 1937.
53. ANDREWS, E., and HRDINA, L. Hepatogenous cholecystitis. *Arch. Surg.*, 23:201-14, 1931.
54. ANDREWS, E., and HRDINA, L. The cause of death in liver autolysis. *Surg. Gynec. Obst.*, 52:61-66, 1931.
55. ANDREWS, E.; HRDINA, L.; and DOSTAL, L. E. Etiology of gallstones. Analysis of duct bile from diseased livers. *Arch. Surg.*, 25:1082-89, 1932.
56. ANDREWS, E.; REWBRIDGE, A. G.; and HRDINA, L. Causation of *Bacillus welchii* infections in dogs by injection of sterile liver extracts or bile salts. *Proc. Soc. Exper. Biol. & Med.*, 28:136-37, 1930; *Surg. Gynec. Obst.*, 53:176-81, 1931.
57. ANDREWS, E.; SCHOENHEIMER, R.; and HRDINA, L. Etiology of gallstones. Chemical factors and the role of the gallbladder. *Arch. Surg.*, 25:796-810, 1932.
58. ANDREWS, E.; THOMAS, W. A.; and SCHLEGEL, K. Newer aspects of liver disease. *Surg. Gynec. Obst.*, 47:179-82, 1928.
59. ANTIĆ, D., and GOROPEVŠEK, M. Über die Toxizität der Galle. *Ztschr. f. d. ges. exper. Med.*, 97:177-85, 1935.

60. ANTITCH, D. (Antić). La Toxicité de la bile. *Compt. rend. Soc. de biol.*, **98**:1145-48, 1928.
61. AOYOMA, T. Zur Frage der Cholelithiasis. *Beitr. z. path. Anat. u. z. allg. Pathol.*, **57**:168-82, 1914.
62. APPEL, B. Sodium dehydrocholate in arsphenamine poisoning. *Arch. Dermat. & Syph.*, **27**:401-7, 1933.
63. APPEL, B., and JANKELSON, J. R. Treatment of arsenical hepatitis with sodium dehydrocholate. *Arch. Dermat. & Syph.*, **32**:422-45, 1935.
64. APPLEBAUM, M., and PATTERSON, M. B. The effect of bile on the bacteriophage phenomenon. *J. Infect. Dis.*, **58**:195-203, 1936.
65. ARBUTHNOT, J. Rules of diet, p. 267. 1732.
66. ARCHIBALD, E. The experimental production of pancreatitis in animals as the result of the resistance of the common duct sphincter. *Surg. Gynec. Obst.*, **28**:529-45, 1919.
67. ARCHIBALD, E. Acute edema of the pancreas. *Ann. Surg.*, **90**:803, 1929.
68. ARCHILOCHUS. 118. *Iambographorum principis relicuiae*. edidit. Lipsiae: Ignatius Liebel, 1818.
69. ARETAEUS, CAPPADOC. On jaundice or icterus. *Libri VII*, Argent 1768, p. 8. FRANCIS ADAMS, *The Extant Works of Aretaeus, the Cappadocian*. London: Sydenham Society, 1856. Pp. 324-28.
70. ARINKIN, M. I. [Alteration of the blood in icterus.] Russian. *Vračebn. gazeta*, St. Petersburg, **13**:1-4, 39-43, 1906.
71. ARMSTRONG, A. R.; KING, E. J.; and HARRIS, R. I. Phosphatase in obstructive jaundice. *Canad. M. A. J.*, **31**:14-20, 1934.
72. ARNOLD, F. *Zur Physiologie der Galle*. Mannheim, 1854. *Physiologische Anstalt der Universität Heidelberg*. 1858.
73. ARONSOHN, H. G. Weisse Galle im Tierexperiment und in der Chirurgie. *Beitr. z. klin. Chir.*, **156**:63-76, 1932.
74. ARONSOHN, H. G. The pathogenesis of white bile. *Arch. Surg.*, **32**:1055, 1936.
75. ARONSOHN, H. G., and ANDREWS, E. Nitrogen content of the bile of normal and diseased gall bladders. *Proc. Soc. Exper. Biol. & Med.*, **33**:85-87, 1935.
76. ARONSOHN, H. G., and ANDREWS, E. Bile salt cholecystitis. *Proc. Soc. Exper. Biol. & Med.*, **33**:87-89, 1935.
77. ARONSOHN, H. G., and ANDREWS, E. Non-bacterial cholecystitis. The mechanism of acidification of bile in the gall bladder. *Proc. Soc. Exper. Biol. & Med.*, **33**:89-91, 1935.
78. ARONSOHN, H. G., and ANDREWS, E. Effects of varying pH on toxic effect of bile salts on the normal gall bladder. *Proc. Soc. Exper. Biol. & Med.*, **34**:763-65, 1936.

79. ASCHOFF, L. Zur Frage der Cholesterinbildung in der Gallenblase. Münch. med. Wchnschr., 2:1847-48, 1906.
80. ASCHOFF, L. Über den Ort der Gallenfarbstoffbildung. Klin. Wchnschr., 3:961-67, 1924.
81. *ASCHOFF, L. Über Bildungs- und Ausscheidungsstörungen der gallenfähigen Substanzen (Dyscholie), besonders des Gallenfarbstoffs (Ikterus). Acta path. & microbiol. Scandinav., 5:338-81, 1928.
82. ASCHOFF, L. Über physiologische und pathologische Gallenfarbstoffbildung. Wien. med. Wchnschr., 80:1011-15, 1930.
83. ASCHOFF, L. Über die verschiedenen Auswirkungen des Bilirubin I und Bilirubin II auf den übrigen Organismus. Med. Klin., 28:1553-54, 1932.
84. ASCHOFF, L., and HUMMEL, R. Beitrag zur Frage des Icterus neonatorum. Virchows Arch. f. path. Anat., 275:1-12, 1929.
85. ASHER, L. Einfluss der Galle auf die Darmbewegung. VII International Physiologen-kongress. Heidelberg, August 1907. Arch. Internationales de Physiologie, in Deutsche med. Wchnschr., 38:1565, 1907.
86. ASHER, L., and SCHEINFINKEL, N. Die Umstimmung pharmakologischer Wirkungen, insbesondere autonomer Nervenendgifte durch oberflächenaktive Stoffe. Biochem. Ztschr., 186:87-94, 1927.
87. ASHUR, L., and BEYELER, K. Beiträge zur Physiologie der Drüsen. Fortgesetzte Untersuchungen über die chemische Regulation des Herzschlages durch die Leber und über die chemische Natur des von der Leber abgegebenen herzregulierenden Hormons. Biochem. Ztschr., 178:351-81, 1926.
88. ASODA, Y. Significance of the liver in the metabolism of lipid bodies. Change in the amounts of lipid bodies in the blood and the bile in parenteral administration of lecithin to normal rabbits. Jap. J. Gastroenterol., 5:115-23, 1933.
89. ASODA, Y. Significance of the liver in the metabolism of lipid bodies. Changes in lipid bodies in the blood and bile when various kinds of bile acids are administered. Jap. J. Gastroenterol., 6:1-6, 1934.
90. ASODA, Y. Calcium diet and bilirubin metabolism. Jap. J. Gastroenterol., 6:51-60, 1934.
91. ASZÓDI, Z. Über den Zuckergehalt der Galle. Biochem. Ztschr., 274:146-53, 1934.
92. ATKIN, E. E. The rationale of the bile solubility of pneumococcus. Brit. J. Exper. Path., 7:167-72, 1926-27.
93. AUGUSTE, C. Action du cholalate de soude la toxine dysentérique; pouvoir antitoxique in vitro. Compt. rend. Soc. de biol., 112:199-200, 1933.

94. AUGUSTE, C. Action du cholalate de soude la toxine dysentérique. Pouvoir antitoxique in vivo. *Compt. rend. Soc. de biol.*, 112:387-88, 1933.
95. AUSTONI, B., and COGGI, G. Considerazioni sul ricambio minerale in un caso di derivazione totale esterna della bile. *Arch. ital. di chir.*, 37:464-72, 1934.
96. AUTENRIETH, J. H. F. *Handbuch d. emp. mensch. Physiologie*. Tübingen, 2:98, 1802.
97. AUVRAY, L. A. Peut-on toujours rapporter l'ictère à la bile ou au principe colorant de la bile circulant avec le sang? Paris, 1811.
98. BABKIN, B. P. Die Galle als Verdauungssekret. *Handbuch der Normalen und Pathologischen Physiologie*, 3:778-803, 1927.
99. BAKES, J. Zur drainagelosen Gallenchirurgie und der methodischen Dilatation der Pupille. *Zentralbl. f. Chir.*, 55:1858-68, 1928.
100. BALDERSTON, S. V. Anaemia associated with biliary fistula. *Arch. Int. Med.*, 50:223-25, 1932.
101. BALDI, D. Recherches expérimentales sur la marche de la sécrétion biliaire. *Arch. ital. de biol.*, 3:389-97, 1883.
102. BALFOUR, D. C., and ROSS, J. W. Postoperative biliary fistulas. *Arch. Surg.*, 3:582-94, 1921.
103. BALTACÉANO, G.; ANGELESEN, H.; and VASILIU, C. Die Wirkung von Octinum auf die Gallensekretion. *Arch. f. exper. Path. u. Pharmacol.*, 177:29-33, 1935.
104. BALTACÉANO, G.; VASILIU, C.; and PARASCHIV, M. H. L'Action de la folliculine sur la sécrétion biliaire. *Compt. rend. Soc. de biol.*, 117:141-43, 1934.
105. BALTACÉANO, G.; VASILIU, C.; and PARASCHIV, M. H. L'Hypophyse antérieure et la sécrétion biliaire. *Compt. rend. Soc. de biol.*, 117:279-83, 1934.
106. BALTACÉANO, G., and VASILIU, C. Recherches sur le sucre biliaire. *Compt. rend. Soc. de biol.*, 121:1114-16, 1936.
107. BALTACÉANO, G., and VASILIU, C. La Sécrétion biliaire et le régime riche en foie. *Compt. rend. Soc. de biol.*, 121:1535-37, 1936.
108. BAMBERGER, H. *Krankheiten des Chylopoëtischen Systems*. Virchows Handb. d. spec. Path. u. Ther. Erlangen, 1857, p. 517; 2e Auflage, 1864, p. 584.
109. BANG, F. La Bilirubinémie considérée spécialement comme symptôme de l'appendicite et des extravasions sanguines. *Gynéc. et Obstét.*, 14:223-32, 1926.
110. BANG, I. Darstellung der Taurochosaure. *Beitr. z. chem. Physiol. u. Path.*, 7:148-49, 1905.

111. BARBÉRA, A. G. L'Élimination de la bile dans le jeûne et après différents genres d'alimentation. *Arch. ital. de biol.*, 23:165-72, 1895.
112. BARIÉTY, M. Des sels biliaires. Méthodes de caractérisation. Etude physio-clinique. Arnette (éd.). Thèse de Paris, 1927.
113. BARLIK, A. Über den Entstehungsmechanismus der Erhöhung des Antiprophthrombinspiegels im Blut beim Stauungsikterus. *Arch. f. klin. Chir.*, 176:656-65, 1933.
114. BARLIK, A. Über das Wesen der verzögerten Blutgerinnung beim Stauungsikterus. *Klin. Wchnschr.*, 13:102, 1934.
115. BARNES, B. O. The excretion of iodine in experimental hyperthyroidism. *Am. J. Physiol.*, 103:699-703, 1933.
116. BARON, J. V. Etude comparative du pouvoir antiseptique de la bile à l'état physiologique et sous l'influence des substances médicamenteuses. Lyon, 1895.
117. BARROW, J. V.; ARMSTRONG, E. L.; and OLDS, W. H. A clinical, pathological and operative study of the icterus index. *Am. J. M. Sc.*, 169:583-94, 1925; 170:519, 1925.
118. BARUK, H.; BRIAND, H.; CAMUS, L.; and CORNU, R. L'Anxiété biliaire. Données cliniques et expérimentales sur l'action de la bile et des sels biliaires sur les centres neuro-végétatifs (en particulier respiratoires). *Ann. méd.-psychol.*, 93:177-92, 1935.
119. BARUK, H., and CAMUS, L. Action neurotrophe expérimentale de biles humaines, recueillies par tubage duodéal, chez le chat, la souris, le pigeon et le cobaye. Sommeil pathologique; stupeur et troubles végétatifs. *Compt. rend. Soc. de biol.*, 116:27-29, 1934.
120. BARUK, H., and CAMUS, L. Catalepsie expérimentale chez le pigeon et la souris par injection sous-cutanée de biles prélenées par tubage duodéal chez deux ictériques. Catalepsie et stupeur biliaires. *Compt. rend. Soc. de biol.*, 116:29-31, 1934.
121. BARUK, H., and CAMUS, L. Action expérimentale des sels biliaires dans la genèse de certains troubles nerveux produits chez l'animal par injections de biles humaines recueillies par tubage duodéal. *Compt. rend. Soc. de biol.*, 116:136-38, 1934.
122. BARUK, H., and CAMUS, L. Sur un principe toxique cataleptisant décelé dans la bile de tubage duodéal de cinq malades atteints d'ictère. Catatonie et ictère. Données expérimentales et cliniques. *Compt. rend. Soc. de biol.*, 116:403-4, 1934.
123. BARUK, H., and CAMUS, L. Les paralysies biliaires expérimentales. *Compt. rend. Soc. de biol.*, 116:405-6, 1934.
124. BARUK, H., and CAMUS, L. Sur une variété de catalepsie biliaire expérimentale. *Ann. méd.-psychol.*, 92:Part 2, 711-43, 1934.

125. BASU, K. P., and CHAKRAVARTY, S. C. Action of *B. coli* on conjugated bile acids. *Indian J. M. Research*, 21:691-94, 1934.
126. BAUER, J., and SPIEGEL, E. Über das Bilirubin im Blute und seine pharmakologische Beeinflussbarkeit. *Deutsches Arch. f. klin. Med.*, 129:17-40, 1919.
127. BAYER, G. Untersuchungen über die Gallenhämolyse. *Biochem. Ztschr.*, 5:368-80, 1907.
128. BAYER, G. Über die Angriffspunkte der Galle bei der Hämolyse. *Biochem. Ztschr.*, 9:58-71, 1908.
129. BAYER, G. Beitrag zur Lehre vom Kreislauf der Galle. Die Schutzwirkung des Serums gegenüber der Giftwirkung der Galle. *Biochem. Ztschr.*, 13:215-33, 1908.
130. BAYER, G. Über die Ursache der Beschleunigung der Gallenhämolyse in konzentrierten Salzlösungen. *Biochem. Ztschr.*, 13:234-42, 1908.
131. BAYER, H. Über die Säuren der menschlichen Galle. *Strassburg*, 1879. *Ztschr. f. physiol. Chem.*, 3:293-311, 1879.
132. BECCARRI, E. Sull'azione fotosensibilizzatrice della bilirubina. *Boll. di Soc. ital. di biol. sper.*, 5:352-56, 1930.
133. BECKMANN, K. Eine neue Methode der Bakterienabtötung in den Gallenwegen bei Cholangitis bzw. Cholezystitis und Bakteriochole. *München. med. Wchnschr.*, 75:2042-43, 1928.
134. BECKWITH, T. D. Viability of *B. typhosus* in alkaline bile in vivo. *Proc. Soc. Exper. Biol. & Med.*, 18:36, 1921.
135. BECKWITH, T. D. Direct injection of *B. typhosus* into the gallbladder. *J. Infect. Dis.*, 31:468, 1922.
136. BECKWITH, T. D., and LYON, R. H. Viability and growth of *B. typhosus* in bile. *J. Infect. Dis.*, 28:62, 1921.
137. BELLATI, L. Über die Giftigkeit des Harns bei Leberkrankheiten. Moleschotts Untersuchungen zur Naturlehre, 15:299, 1895.
138. BELLIER, C. Contribution à l'étude des souffles cardiaques dans l'ictère. *Paris*, 1894.
139. BELLINI, L. Opuscula aliquot—de motu bilis, pp. 147-80. *Lugduni Batavorum: Apud S. Luchtmanns*, 1737.
140. BELOUSSOW, P. N. Über die Folgen der Unterbindung des Ductus Choledochus. *Arch. f. exper. Pathol. u. Pharmacol.*, 14:200-211, 1881.
141. BÉNARD, H., and BARIÉTY, M. Les Sels biliaires ont-ils une action bradycardisante? *Compt. rend. Soc. de biol.*, 98:1397-98, 1928.
142. BENCsik, F.; GASPÁR, A.; VERZÁR, F.; and ZIH, A. Weitere Untersuchungen über die Wirkung von Bilirubin auf die Zahl der roten Blutkörperchen. *Biochem. Ztschr.*, 225:278-85, 1930.

143. BENEDICT, E. B.; STEWART, C. P.; and CUTNER, P. N. Role in high intestinal obstruction. *Surg. Gynec. Obst.*, 54:605-12, 1932.
144. BENSLEY, E. H. The renal threshold of bilirubin. *J. Biol. Chem.*, 103:71-79, 1933.
145. BERBÉRA, A. G. L'Azote et l'eau dans la bile et dans les urines. (Thèse de Doctorat.) *Arch. ital. de biol.*, 20:139-48, 1893.
146. BERG, B. N. Peptic ulcers. Comparative frequency after deprivation of bile and pancreatic juice. *Arch. Surg.*, 28:1057-60, 1934.
147. BERG, B. N., and JOBLING, J. W. Biliary and hepatic factors in peptic ulcers. An experimental study. *Arch. Surg.*, 20:997-1015, 1930.
148. BERGH, B. N.; ZAW, Z. D.; and JOBLING, J. W. Bactericidal function of liver. *Proc. Soc. Exper. Biol. & Med.*, 21:433, 1927.
149. BERG, B. N., and ZUCKER, T. F. Comparative frequency of peptic ulcers after deprivation of bile and pancreatic juice. *Proc. Soc. Exper. Biol. & Med.*, 30:330-32, 1932.
150. BERG, J. Studien über die Function der Gallenwege unter normalen und gewissen abnormen Verhältnissen. *Acta chir. Scandinav.*, 2: Suppl., 1922. Pp. 185.
151. BERGH, G. S.; SANDBLOM, P.; and IVY, A. C. Effects of removal of the functioning gall bladder. *Surg. Gynec. Obst.*, 62:811-14, 1936.
152. BERMBACH, P. Versuche mit Galle und Gallenimmunserum. *Arch. ges. Physiol., Bonn*, 118:205-14, 1907.
153. BERNARD, CL. Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme, 2:188-200. Paris: J. B. Baillière et Fils, 1859.
154. BERNHARD, F. Die Bedeutung der weissen Galle für die Chirurgie nach 25 klinischen Beobachtungen bei Operationen und auf Grund von erfolgreichen Versuchen, den Hydrops der Gallenwege im Tierexperiment zu erzeugen. *Deutsche Ztschr. f. Chir.*, 222:66-91, 1930; abstr., *Zentralbl. f. Chir.*, 57:194-96, 1930.
155. BERNHARD, F. Weitere klinische und experimentelle Beobachtungen über die Bedeutung und Entstehung des Hydrops der Gallenwege oder der sog. weissen Galle. *Beitr. z. klin. Chir.*, 154:389-425, 1932.
156. BERNHARD, F. Zur Frage der Höhensonnenbestrahlung gegen die Gefahr der cholaemischen Blutung. *Chirurg*, 6:704-6, 1934.
157. BERNHEIM, A. R. The icterus index. *J.A.M.A.*, 82:291-95, 1924.
158. BERNHEIM, A. R. Bilirubinaemia: significance of variations. *Arch. Path.*, 58:747, 1926.
159. BERTI, A. Sull'azione locale della bile e del glicocolato di soda sui vasi sanguigni. *Atti del r. Ist. ven. di sc. lett. ed arti.*, 67:357, 1907-8.

160. BERTI, A. Azione della bile sui movimenti ritmici e sul tono del l'intestino. Arch. di fisiol., 6:306-14, 1909, .
- 161.*BERTI, A., and BERNUCCI, F. Il Progresso del cibo lungo il tubo digerente quando eccede e quando difetta la bile. Arch. di farmacol. sper., 27:134, 1919.
162. BERTI, A., and MALESANI. Azione della bile sull' attività diastolica del cuore. Arch. ital. de biol., 1910, p. 101.
163. BERZELIUS, J. Über die Zusammensetzung der Galle. Ann. d. Chem., 33:139-79, 1840.
- 164.*BERZELIUS, J. J. Galle. In Wagner's Handwörterbuch der Physiologie, 1:516-27, 1842.
165. BESREDKA, M. Vaccination par voie buccale [Bile sensitization]. Paris méd., 43:460-63, 1922.
166. BETTMANN, H. W. Diseases of the liver. In Blumer edition of Billings-Forchheimer's Therapeutics of internal diseases, 4:712-51, 1924. New York: D. Appleton.
167. BETZ, W. Über den Blutstrom in der Leber, insbesondere den in der Leberarterie. Sitzungsber. k. Akad. Wissensch. Math.-Naturw. Cl., Wien., 46:238-54, 1863.
168. BEUTTENMÜLLER, H. Toxigene Osteoperiostitis ossificans bei chronischem Icterus. Berl. klin. Wchnschr., 45:1001-4, 1908.
169. BEYERS, A. Urobilinurie und Ikterus bei unseren pflanzenfressenden Haustieren. Diss. Utrecht, 1923.
170. BIAL, M. Über den Befund von gepaarter Glukoronsäure in der Galle. Ztschr. f. physiol. Chem., 65:258-64, 1905
- 171.*BIANCHI, J. B. Historia hepatica. Tomus primus et tomus alter. Genevae: Apud Gabrielem de Tournes et Filios, 1725.
172. BICKEL, A. Action de la bile et des sels biliaires sur le système nerveuse. Compt. rend. Soc. de biol., 124:702, 1895.
173. BICKEL, A. Experimentelle Untersuchungen über den Einfluss der Galle und der gallensäuren Salze auf das Central-nervensystem. München. med. Wchnschr., 44:553-54, 1897.
174. BICKEL, A. Über die krampferregende Wirkung der Galle und der gallensäuren Salze. Verhandl. d. 18 Kong. f. inn. Med., 1900, pp. 445-49.
175. BICKEL, A. Experimentelle Untersuchungen über die Pathogenese der Cholaemie. Wiesbaden, 1900. Pp. 112.
- 176.*BIDDER, F., and SCHMIDT, C. Die Verdauungssäfte und der Stoffwechsel. Eine physiologisch-chemische Untersuchung. Mitau und Leipsic, 1852. Pp. 212.
177. BIEDL, A., and KRAUS, R. Über eine bisher unbekannte tonische Wirkung der Gallensäuren auf das Centralnervensystem. Zentralbl. f. inn. Med., 19:1185-1200, 1898.

178. BIERTHEN, E. Untersuchungen über das Vorkommen des Bilirubins in der Galle, in dem Harn und Blutserum des Pferdes. Hannover, 1906; also *Deutsche tierärztl. Wchnschr.*, 14:481, 497, 1906.
179. BILLANDOT, M., and MATTHIEU, J. Relation entre cholestérine et bilirubine dans les ictères. *Compt. rend. Soc. de biol.*, 103:878-79, 1930.
180. BILLI, A., and GRECO, T. Contributo allo studio sperimentale delle cosiddette peritoniti e all'influenza su di esse della vagotomia. *Clin. chir.*, 10:42, 1934.
181. BINET, L., and PERLÈS, L. Sur la bradycardie ictérique. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 53:981, 1929.
182. BIRCH-HIRSCHFELD, F. R. Die Entstehung der Gelbsucht neugeborener Kinder. *Virchows Arch. f. path. Anat.*, 87:1-38, 1882.
183. BISCHOFF, E. Über den Nachweis der Gallensäuren mittelst der Pettenkofer'schen Probe und über das Vorkommen dieser Säuren im ikterischen Harn. *Ztschr. f. rat. Med.*, 3d ser., 21:125-52, 1864.
184. BISSELL, A. D., and ANDREWS, E. Acholic cachexia. *Arch. Surg.*, 32:624-68, 1936.
185. BISSO, A. La Tossicità dell'urina prima e dopo la legatura della vena porta. *Istituto di farmacologia sperimentale*, 3:151-92, 1896.
186. BISSO, A. Die Toxizität des Harns vor und nach der Unterbindung der Vena portae. *Moleschotts Untersuchungen zur Naturlehre des Menschen und der Thiere*, 16:90-130, 1899.
187. BIX, H. Decholin als Diuretikum. *Wien. klin. Wchnschr.*, 40:321-22, 1927.
188. BLAD, A. Studien über Gallenperitonitis ohne Perforation der Gallenwege. *Arch. f. klin. Chir.*, 109:101-20, 1918.
189. BLALOCK, A. A clinical study of biliary tract disease. *J.A.M.A.*, 83:2057-60, 1924.
190. BLANCK, E. E. Peptic ulcer. *Surg. Gynec. Obst.*, 61:480-93, 1935.
191. BLANKENHORN, M. A. Bile content of the blood in pernicious anaemia. *Arch. Int. Med.*, 19:344-53, 1917.
192. BLANKENHORN, M. A. The distribution of bile in certain types of jaundice. *Arch. Int. Med.*, 21:282, 1918.
193. BLANKENHORN, M. A. Acholuric jaundice. *Arch. Int. Med.*, 27:131-34, 1921.
194. BLANKENHORN, M. A. Absorption of bile pigments from the intestines. *J. Exper. Med.*, 45:199-202, 1927.
195. BLANKENHORN, M. A. Blood urobilin. *J. Biol. Chem.*, 80:477-85, 1928.
196. BLANKENHORN, M. A. Clinical significance of jaundice. *J.A.M.A.*, 95:1066-68, 1930.

197. BLAY, V. Experimental Untersuchung über die Wirkung des gallensäuren Natrons auf die Herztätigkeit. Inaug.-Diss. Erlangen, 1877.
198. BLOND, K. Wandlungen in der Lehre von der Funktion der Gallenwege. Arch. f. klin. Chir., 170:597-647, 1932.
199. BLONDLOT, N. Essai sur les fonctions du foie. Paris et Nancy, 1846.
200. BLONDLOT, N. Inutilité de la bile dans la digestion proprement dite. Nancy, Mém. Soc. sci., 1851, pp. 50-63; Compt. rend. Soc. de biol., 32:904-6, 1851.
201. BLOOM, W. The rôle of the lymphatics in the absorption of bile pigment from the liver in early obstructive jaundice. Bull. Johns Hopkins Hosp., 34:316-20, 1923.
202. BOAS, F. Zur Kenntnis der Wirkung von Gallensalzen auf die Zelle. Protoplasma, 9:428-40, 1930.
203. BOBBIO, A., and ZILLOCCI, E. Studio sugli effetti dell'intervento operatorio riguardo la composizione della bile. Arch. ital. di chir., 38:741-74, 1934.
204. BOCK, E. Zum Problem der Gallenfarbstoffbildung und des Ikterus. Klin. Wchnschr., 3:587-92, 638-41, 1924.
205. BOERHAAVE, HERMANN. Praxis medica: Commentarius in aphorismos. Patav., 1728. Opuscula omnia. Hagae, 1738.
206. BOGOMOLOFF, T. [On the relation of chromogenic biliary acids to the pigment of the urine and excreta.] Russian. St. Petersburg, 1871.
207. BOLLMAN, J. L. Experimental studies on hepatic alterations. Proc. Staff Meet. Mayo Clinic, 11:727-28, 1936.
208. BOLLMAN, J. L., and MANN, F. C. Experimentally produced lesions of the liver. Ann. Int. Med., 5:22, 1931.
209. BOLLMAN, J. L., and MANN, F. C. Peptic ulcer in experimental obstructive jaundice. Arch. Surg., 24:126-35, 1932.
210. BOLLMAN, J. L., and MANN, F. C. The van den Bergh reaction in the jaundice following complete removal of the liver. Arch. Surg., 24:675-80, 1932.
211. BOLLMAN, J. L., and MANN, F. C. The influence of the liver on the destruction of bile salt. Arch. Path., 16:304, 1933.
212. BOLLMAN, J. L., and MANN, F. C. The influence of the liver in the formation and destruction of bile salts. Am. J. Physiol., 116:214-24, 1936.
213. BOLLMAN, J. L.; MANN, F. C.; and DUPAGE, P. The effect of specific cholecystitis on the bile-concentrating activity of the gallbladder. J. Lab. & Clin. Med., 10:544-47, 1925.
214. BOLLMAN, J. L.; SHEARD, C.; and MANN, F. C. The absorption of bile pigment from the intestines. Am. J. Physiol., 78:658-65, 1926.

215. BOLLMAN, J. L.; SHEARD, C.; and MANN, F. C. An experimental study of obstructive jaundice with particular reference to the initial bilirubinemia. *Am. J. Physiol.*, 80:461-64, 1927.
216. BOMBI, G. La Peritonite biliare senza perforazione apparente della vie biliari. *Arch. ital. di chir.*, 39:425, 1935.
217. BOMTEMPS, H. Darstellung der Glykocholsäure aus Rindergalle. Fallende Wirkung der Uransalze auf Gallensäuren. *Diss. Greifswald*, 1905.
218. BONANNO, G. Ricerche sperimentali su taluni fermenti della bile. *Arch. di farmacol. sper.*, 7:466-88, 1908.
219. BONANNO, G. Sur l'augmentation des résistances des globules rouges au cours de l'ictère. Etude expérimental. *Folia haemat.*, 7:117-20, 1909.
220. BONAR, B. D. The icterus index in the new-born infant. *Am. J. Dis. Child.*, 50:1143-51, 1935.
221. BONDI, S. Beiträge zur Chemie der Galle. *Ztschr. f. physiol. Chem.*, 53:8-13, 1907.
222. BONDI, S. Protokoll—Gesellschaft der Aerzte in Wien. *Wien. klin. Wchnschr.*, 21:271, 1908.
223. BONDI, S., and MÜLLER, E. Synthese der Glykocholsäure und Tau-rocholsäure. *Ztschr. f. physiol. Chem.*, 47:499-506, 1906.
224. BORCHARDT, H. Über das Vorkommen von Gallensäuren beim Ikterus und dem Ikterus Dissociatus. *Klin. Wchnschr.*, 1:988-91, 1922.
225. BORCHARDT, H. Weitere Beobachtungen und Erfahrungen über Gallensäuren bei Ikterus im Harn, Blut, Duodenalsaft und Liquor Cerebro-spinalis. *Klin. Wchnschr.*, 2:541-42, 1923.
226. BORDIER, MOREL, and NOGIER. Action des radiations de la lampe à vapeurs de mercure sur la bile et l'urobiline. *Lyon méd.*, 111:173, 1908.
227. BORSCHKE, W., and FRANK, R. Untersuchungen über die Konstitution der Gallensäuren. *Ber. d. deutsch. Chem.*, 60:726, 1927.
228. BOSSA, G. Influenza delle intossicazioni del fegato sulla composizione chimica della bile. *Riforma med.*, 45:1303-5, 1929.
229. BOTTIN, J. La Méthode de choix pour l'étude de la pression intracholécystique chez le chien. *Compt. rend. Soc. de biol.*, 118:1642-45, 1935.
230. BOUCHARD, C. Leçons sur les autointoxications dans les maladies. Paris, 1887.
231. BOUCHARD, C. Leçons sur les maladies par ralentissement de la nutrition. Paris, 1890.
232. BOUCHARD, C. Auto-intoxication in disease. THOMAS OLIVER (tr.). Philadelphia: F. A. Davis Co., 1894.
233. BOUCHARD, C. Traité de pathologie générale, 1:780, 1895.

234. BOUCKAERT, J. J., and APPELMANS, R. La Courbe de disparition de la bilirubine injectée chez le chien par voie intraveineuse. *Compt. rend. Soc. de biol.*, 93:843-45, 1925.
235. BOUCKAERT, J. J., and SAADI-NAZIM. Sécrétion biliaire après injection de sels decalcifiants. *Compt. rend. Soc. de biol.*, 97:359-60, 1927.
236. BOUDEILLE, T. Influence de la bile sur les fermentations coli-bacillaires. *Compt. rend. Soc. de biol.*, 72:783-85, 1912.
237. BOUISSON, F. De la bile, de ses variétés physiologiques, de ses altérations morbides. *J. Soc. de méd-prat. de Montpel.*, 4:352, 1841; 5: 191, 1842; 6:180, 254, 419, 1843.
238. BOUISSON, F. De la bile. Montpellier, 1843.
239. BOUISSON, H. F. De la bile. De ses variétés physiologiques, de ses altérations morbides. Paris: Louis Castel, libraire editeur, 1843. Pp. 308.
240. BOUISSON, F. Die Galle im gesunden und krankhaften Zustande. Anhang: Zur Physiologie der Galle nach N. Blondiot und E. A. Platner. Wien, 1847. 2 vols.
241. BOURGEOISE, F. T. M. De l'ictère. Paris, 1814.
242. BOWLER, J. P. The management of obstructive jaundice as a factor affecting surgical risk. *Boston M. & S. J.*, 193:1045, 1925.
243. BOWLER, J. P., and WALTERS, W. Toxicity and rate of excretion of calcium chloride from the blood stream. *Ann. Surg.*, 80:545-50, 1924.
244. BOYCE, F. F., and McFETRIDGE, E. M. So-called "liver deaths": a clinical and experimental study. *Arch. Surg.*, 31:105-36, 1935; 32: 1080-86, 1936.
245. BOYD, W. Studies in gall-bladder pathology. *Brit. J. Surg.*, 10:337-56, 1923.
246. BRACKWERTZ, W. Gleichzeitiges Vorkommen von perforationsloser Gallen- und Bauchspeichelperitonitis ohne Erkrankung des Pankreas, zugleich ein Beitrag zur Frage der Pankreasfermentschädigung der Gallenwege. *Arch. f. klin. Chir.*, 168:665-82, 1932.
247. BRACKERTZ, W. Tierexperimentelle Untersuchungen an den extrahepatischen Gallenwegen. *Deutsche Ztschr. f. Chir.*, 243:614-20, 1934.
248. BRACONNOT, H. Recherches sur la bile. *Ann. de chim. et phys.*, 42: 171-85, 1829.
249. BRADLEY, H. C., and TAYLOR, J. The influence of bile on autolysis. *J. Biol. Chem.*, 29:281-88, 1917.
250. BRAEYE, L. Study of the toxic absorption from intestinal tract in experimental high obstruction. *Bull. Johns Hopkins Hosp.*, 40:33-39, 1927.

251. BRAID, F. Osseous dystrophy following icterus gravis neonatorum. *Arch. Dis. Childhood*, 7:313-20, 1932.
252. BRAKEFIELD, J. L., and SCHMIDT, C. L. A. Studies on the synthesis and elimination of certain bile components in obstructive jaundice. *J. Biol. Chem.*, 67:523-45, 1926.
253. *BRAND, J. Beitrag zur Kenntnis der menschlichen Galle. *Arch. f. d. ges. Physiol.*, 90:491-522, 1902.
254. BRANDENBERG, K. Über die Wirkung der Galle auf das Herz und die Entstehung der Pulsverlangsamung beim Icterus. *Berl. klin. Wchnschr.*, 40:865-68, 1903.
255. BRANDENBERG, K. Über die Wirkung der Galle auf das Herz. *Engelmanns Arch. f. Physiol.*, 1903, Suppl., pp. 144-91.
256. BRATIANU, S.; SOLOMON, E.; and BRATIANU, T. Action du déhydrocholate de soude sur la cellule hépatique du lapin. *Compt. rend. Soc. de biol.*, 112:1494-96, 1933.
257. BRAUER, L. Über pathologische Veränderungen der Galle. *München. med. Wchnschr.*, 48:1003-5, 1901.
258. BRAUN, F. G. [Action of bile on several forms of microbes.] Russian. St. Petersburg, 1899.
259. BRAUN, L., and MAYER, W. Über die Wirkung der Galle und der Gallensäuren Salze auf das isolierte Säugetierherz. *Sitzungsbr. Math.-Naturwissenschaft, Wien.*, 108: Abtl. III, 559, 1899.
260. BREUSCH, F. Neue Methode der Gallenanalyse. *Ztschr. f. physiol. Chem.*, 227:242-46, 1934.
261. BREUSCH, F., and JOHNSTON, C. G. Zum Verschwinden und Wiederscheinen der Gallensäuren in der Galle bei vorübergehendem Choleochusverschluss. *Klin. Wchnschr.*, 13:1856-57, 1934.
262. BRIGL, P., and BENEDICT, O. Über die Nutria-Gallensäure. *Ztschr. f. physiol. Chem.*, 220:106-12, 1933.
263. BRÖCHNER-MORTENSEN, K. Über Bilirubinbelastung als Leberfunktionsprobe. *Acta med. Scandinav.*, 85:1-32, 1935.
264. BROCC, P. Les Pancréatites aiguës chirurgicales. Paris: Masson et Cie, 1926. Pp. 188.
265. BROCC, P., and MOREL, L. Le Rôle de la bile dans la reproduction expérimentale des pancréatites hémorragiques avec stéatonecrose. *Compt. rend. Soc. de biol.*, 82:371-72, 1919.
266. BRODIE, BENJAMIN, SIR. Observations on the effects produced by the bile in the process of digestion. *Quart. Jr. of Sc. Lit. and Arts.*, 14: Ser. T, 341-44, 1823.
267. BRONNER, H. Der Einfluss der Ernährung auf die Wasserstoffionenkonzentration der Galle. *Klin. Wchnschr.*, 12:1562-63, 1933.
268. BRONNER, H. Wasserstoffionenkonzentration der Galle und Steinbildung. *Arch. f. klin. Chir.*, 180:597-99, 1934.

269. BROWN, G. O.; McMASTER, P. D.; and ROUS, P. The enterohepatic circulation of bile pigment. *J. Exper. Med.*, 37:699-710, 1923.
270. BROWN, G. O.; McMASTER, P. D.; and ROUS, P. The relation between blood destruction and the output of bile pigment. *J. Exper. Med.*, 37:733-57, 1923.
271. BROWN, A. L. Rapid clinical method for the determination of the icterus index. *Arch. Path.*, 3:409-10, 1927.
272. BROWN, J. G. Notes on the action of bile salts on the animal economy. *Proc. Roy. Soc. Edinburgh*, 8:525-34, 1875.
273. BRÜCKE, E. T. Über Versuche, den Harn einer Niere dauernd in das Blut zu leiten. *Wien. klin. Wchnschr.*, 39:1058-59, 1926.
274. BRUGSCH, T. Zur Analyse des Ikterus. *Deutsche med. Wchnschr.*, 55:687-728, 1929.
275. BRUGSCH, T., and FRÄNKEL, E. Fettsäurenresorption und Galle. *Ztschr. f. d. ges. exper. Med.*, 43:716, 1924.
276. BRUGSCH, T., and HORSTERS, H. Cholereze und Choleretica. *Klin. Wchnschr.*, 2:1538-39, 1923.
277. BRUGSCH, T., and HORSTERS, H. Cholereze und Choleretica. *Ztschr. f. d. ges. exper. Med.*, 38:368-97, 1923.
278. BRUGSCH, T., and HORSTERS, H. Cholereze und Choleretica. *Ztschr. f. d. ges. exper. Med.*, 43:716, 1924.
279. BRUGSCH, T., and HORSTERS, H. Cholagoga und Cholagogie. *Arch. f. exper. Path. u. Pharmakol.*, 118:267-91, 1926.
280. BRUGSCH, T., and HORSTERS, H. Cholagoga und Cholagogie. Die Resorptionsgrösse der Gallenblase. *Arch. f. exper. Path. u. Pharmakol.*, 118:292-304, 1926.
281. BRUGSCH, T., and HORSTERS, H. Cholagoga und Cholagogie. Über den Einfluss peroral zugeführter Salzlösungen auf die Gallenblase; nach experimentellen Untersuchungen. *Arch. f. exper. Path. u. Pharmakol.*, 118:305-12, 1926.
282. BRUGSCH, T., and RETZLAFF, K. Blutzergalle, Galle und Urobilin. Zur Frage der Gallenfarbstoffbildung aus Blut. *Ztschr. f. exper. Path. u. Therap.*, 11:508-25, 1912.
283. BRUGSCH, T., and ROTHER, J. Die Rolle der Galle in Harnsäurestoffwechsel. *Klin. Wchnschr.*, 2:1495-96, 1922.
284. *BRULÉ, M. *Recherches sur les ictérus*. 3d ed. Paris, Masson et Cie, 1922. Pp. 280.
285. BRULÉ, M., and GARBAN. La Retention des sels biliaires dans les affections du foie sans ictère. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 30:407, 1914. *Zit. Nach Kongresszentralbl.*, 9:503, 1914.
286. BRULÉ, M., and GARBAN. Etude critique de la théorie entérohépatique de la uribilinurie. *Rev. méd.*, Paris, 38:583, 1921.

287. BRULÉ, M., and GILBERT-DREYFUS. Recherche des sels biliaires dans les urines albumineuses. *Compt. rend. Soc. de biol.*, 95:1036-38, 1926.
288. BRULÉ, M. H., and LE GALLA SALLE. Les Retentions biliaires latentes dans certaines lésions toxiques et infectieuses du foie. *Zentralbl. f. inn. Med.*, 11:622, 1914.
289. BRULÉ, M. H., and WEISSMANN, Ch. L'Etude de la bilirubine du sérum peut-elle aider à reconnaître la nature d'un ictère. *Presse méd.*, 1922, p. 986.
290. BRULÉ, M. H., and WEISSMANN, Ch. Sur la recherche de l'urobiline dans le sang et dans la bile. *Compt. rend. Soc. de biol.*, 87:138, 1922.
291. BRUNO, J. Über die Injection von Giften ins Gehirn. *Deutsche med. Wchnschr.*, 25:369-72, 1899.
292. BUCHANAN, J. J. Bile peritonitis without evident perforation of the biliary tract. *Surg. Gynec. Obst.*, 26:303, 1918.
293. BUCHBINDER, W. C. Experimental obstructive jaundice. Age factor in the production of bradycardia. *Arch. Int. Med.*, 42:743, 1928.
294. BUCHBINDER, W. C., and KERN, R. The effect of thyroparathyroidectomy on the jaundiced animal. *Proc. Soc. Exper. Biol. & Med.*, 25:3, 1927.
295. BUCHBINDER, W. C., and KERN, R. Experimental obstructive jaundice. *Arch. Int. Med.*, 40:900, 1927.
296. BUCHBINDER, W. C., and KERN, R. Blood calcium deficiency and bone changes in experimental obstructive jaundice. *Am. J. Physiol.*, 81:468, 1927.
297. BUCHBINDER, W. C., and KERN, R. Experimental obstructive jaundice. A modification of the tetany mechanism in jaundice. *Arch. Int. Med.*, 41:754, 1928.
298. BUDD, GEORGE. Die Krankheiten der Leber. E. H. Hensch (tr.). Berlin: Hirschwald, 1846.
299. BUDD, G. Diseases of the liver. London: John Churchill, 1852. Pp. 486.
300. BUDGE, J. Die Galle als starkes Reizmittel für Nerven und Muskeln. *Tagesberichte über die Fortschritte der Natur- und Heilkunde*, 475:343, 1852.
301. BUDGE, J. Spezielle Physiologie des Menschen. Weimar, 1856.
302. BUNDSCHUH, E. Zur perforationlosen Gallenperitonitis. *Arch. f. klin. Chir.*, 161:549-57, 1930.
303. BUNTING, C. H., and BROWN, W. H. The pathology of intraperitoneal bile injections in the rabbit. *J. Exper. Med.*, 14:445-52, 1911.
304. BURDEN, V. G. Observations on the histologic and pathologic anatomy of the hepatic, cystic, and common bile ducts. *Ann. Surg.*, 82:584-697, 1925.

305. BURKE, C. F., and WEIR, J. F. Hemorrhagic tendency in jaundice. *J. Lab. & Clin. Med.*, 18:657-68, 1933.
306. BURTON-OPITZ, R. The viscosity of bile. *Biochem. Bull.*, 3:351-56, 1914.
307. BUTKIEWICZ, T. Die gallige Bauchfellentzündung ohne Perforation der Gallenwege. *Arch. f. klin. Chir.*, 185:55-140, 1936.
308. BUTSCH, W. L.; MCGOWAN, J. M.; and WALTERS, W. Clinical studies on the influence of certain drugs in relation to biliary pain and to the variations in intrabiliary pressure. *Surg. Gynec. Obst.*, 63:451-56, 1936.
309. CABOT, R. C. Differential diagnosis (3d ed.), 1:719. Philadelphia and London: W. B. Saunders & Co., 1915.
310. CADET. Expériences chimiques sur la bile de l'homme et des animaux. *Hist. Acad. roy. d. sc.*, 1767, Part 1770, pp. 471-83.
311. CALALB, G. Action de la bile sur le bactériophage et importance de cette action. *Compt. rend. Soc. de biol.*, 92:1442-43, 1925.
312. CALZAVARA, D. Ricerche sperimentali intorno alla necrosi acute del pancreas. *Arch. ital. di chir.*, 12:429-71, 1925.
313. CAMERON, A. L., and NOBLE, J. F. Reflux of bile up the duct of Wirsung caused by an impacted biliary calculus. *J.A.M.A.*, 82:1410-14, 1924.
314. CAMERON, G. R. Liver regeneration and biliary obstruction. *J. Path. & Bact.*, 41:283-88, 1935.
315. CAMERON, G. R., and OAKLEY, C. L. Ligation of common bile duct. *J. Path. Bact.*, 35:769-98, 1932.
316. CAMPBELL, J. M. H., and WARNER, E. C. Heredity in acholuric jaundice. *Quart. J. Med.*, 75:333, 1926.
317. CANJOLLE, F. L'Elimination biliaire du cobalt. *Bull. Soc. chim. biol.*, 18:1081-90, 1936.
318. CANTAROW, A.; GARTMAN, E.; and RICCHIUTI, G. Hepatic function. *Arch. Surg.*, 30:865-74, 1935.
319. CANTAROW, A., and NELSON, J. Serum phosphatase in jaundice. *Arch. Int. Med.*, 59:1045, 1937.
320. CANTAROW, A., and STEWART, H. L. Alteration in serum bilirubin and bromsulphalein retention in relation to morphological changes in the liver and bile passages in cats with total biliary stasis. *Am. J. Path.*, 11:561-81, 1935.
321. CANTAROW, A., and STEWART, H. L. Hepatic changes on injection of sodium dehydrocholate in cats with total bile stasis. *Arch. Path.*, 22:373-88, 1936.
322. CANTONI, V. L'Azione della bile sui movimenti uterini. *Arch. di farmacol.*, 17:178-86, 1914.

323. CARLSON, A. J. Control of hunger in health and disease. Chicago: University of Chicago Press, 1916.
324. CARR, J. L., and FOOTE, F. S. Progressive obstructive jaundice. Changes in certain elements of the blood and their relation to coagulation. *Arch. Surg.*, 29:277-96, 1934.
325. CARRAVETTA, M. La Secrezione biliare nella eliminazione dei germi e l'impiego terapeutico della bile. *Rinn. med.*, Napoli., 11:264-67, 1926.
326. CARRIÉ, P. A. Les Syndromes ictériques. Paris: Gaston Doin & Cie, 1930.
327. CARRIL, M. J.; VERGNOLLE, M. J.; and DIAZ BOBILLO, I. Ictericia y malfomación congénita de vías biliares. *Rev. Asoc. méd. argent.*, 9:145-51, 1935.
328. CATALANOTTI, V. Lo Stato attuale delle nostre conoscenze sulla biligenesi. *Rassagna internaz. di clin. e terap.*, 15:90-96, 1934.
329. CATO, MARCUS PORCIUS. *De re rustica* 156-4. Lipsiae: Henricus Jordan, 1860.
330. CAVALLARO, V. Sull'azione dei sali biliari. *Gior. di clin. med.*, 13: 224-28, 1932.
331. CAVAZZA, F. Su di alcune ricerche biochimiche nel sangue. Nella bile e nel fegato di animali con fistola biliare permanente. *Pathologica*, 27:241-50, 1935.
332. CAYLOR, H. D., and BOLLMAN, J. L. The bilirubin content of gall-bladder bile in cholecystic disease. *Arch. Path. & Lab. Med.*, 3:993-1001, 1927.
333. CELSUS, A. CORNELIUS. *Medicine: Of the jaundice and its cure*, 3:chap. xxiv, 171-72. JAMES GREIVE (tr.). London: Wilson & Durham, 1756.
334. CEZAN, L. A. An corporis balsamum bilis? Parisiis, 1764.
335. CHABROL, E. Les Pancréatites dans les affections du foie. Thèse inaugurale de doctorat en médecine, 1910.
336. CHABROL, E. Les Polycholies. Etude clinique et expérimentale. *Paris méd.*, 1:469-77, 1931.
337. CHABROL, E. Les Ictères. Paris: Masson et Cie, 1932, Pp. 523.
338. CHABROL, E., and BÉNARD, H. Les Ictères. *Actualités méd.*, J. B. Baillièrre et fils, 1:16, 1921.
339. CHABROL, E., and BÉNARD, H. Cholémie saline et cholestérinémie. *Gaz. des hôp.*, 94:437-45, 1921.
340. CHABROL, E., and BÉNARD, H. L'ictère est-il un signe d'insuffisance du foie? *La méd.*, 3:781-83, 1921-22.
341. CHABROL, E., and BÉNARD, H. Recherches sur la physiopathologie des ictérus cholémie saline et cholestérinémie. *Kongr.-Zentralbl. f. d. ges. inn. Med.*, 21:322, 1922.

342. CHABROL, E.; BÉNARD, H.; and BARIÉTY, M. Etude comparative des pigments, des sels biliaires et de la cholestérine dans un cas de fistule du cholédoque. Bull. et mém. Soc. d. hôp. de Paris, 1:992-94, 1926.
343. CHABROL, E.; BÉNARD, H.; and BARIÉTY, M. Recherches sur les sels biliaires en pathologie hépatique. Thèse de Bariéty. Presse méd., 36:849-52, 1928.
344. CHABROL, E.; CHARONNAT, R.; COTTET, J.; and CACHIN, M. Le Chlore biliaire. Presse méd., 42:1660-62, 1934.
345. CHABROL, E., and CHARONNAT, R. Les Agents thérapeutiques de la sécrétion biliaire. Ann. de méd., 37:131-42, 1935.
346. CHABROL, E.; CHARONNAT, R.; MAXIMIN, M.; and BOCQUENTIN, A. Variations de la sécrétion biliaire sous l'influence des alcaloïdes modificateurs du système nerveux végétatif. Compt. rend. Soc. de biol., 102:754-55, 1929.
347. CHABROL, E.; CHARONNAT, R.; MAXIMIN, M.; and COTTET, J. Recherches sur le mécanisme d'action des hypertensions biliaires expérimentales. Compt. rend. Soc. de biol., 111:693-95, 1932.
348. CHABROL, E.; COTTET, J.; and SALLET, J. Le Mécanisme régulateur de la cholalémie. Paris méd., 99:428-31, 1936.
349. CHABROL, E.; COTTET, J.; and SALLET, J. Recherches comparatives sur le pouvoir de concentration du foie et du rein vis-à-vis de l'acide cholalique. Compt. rend. Soc. de biol. 122:184-86, 1936.
350. CHABROL, E.; COTTET, J.; and SALLET, J. Recherches sur l'enrichissement du foie et du muscle en acide cholalique au cours des cholalémies expérimentales. Compt. rend. Soc. de biol., 122:186-88, 1936.
351. CHABROL, E., and MAXIMIN, M. Recherches sur la cholémie saline. Paris méd., 1:444-49, 1928.
352. CHABROL, E., and MAXIMIN, M. Recherches sur l'élimination des sels biliaires au cours des cholémies salines expérimentales. Rev. méd.-chir. d. mal. du foie, 5:9-33, 1930. Thèse de Maximin, 1929.
353. CHAMBERLAIN, E. N. The cholesterol content of normal tissues and the effect of intravenous injections of cholesterol thereon. J. Physiol., 66:249-61, 1928.
354. CHARCOT, J. M. Leçons sur les maladies du foie. 2d ed. Progrès médical. Paris, 1877.
355. CHARLET, M. Der Gehalt des Blutes an Gallensäuren unter verschiedenen physiologischen Bedingungen. Biochem. Ztschr., 210:42-69, 1929.
356. CHAUFFARD, A. Les Dissociations des états cholémiques. Presse méd., Paris, 21:81-83, 1913.
357. CHAUFFARD, A.; LAROCHE, G.; and GRIGAUT, A. Recherches sur l'origine de la cholestérine biliaire. Comp. rend. Soc. de biol., 74:1005-7, 1913.

358. CHEVREUL, M. Examen des graisses d'homme, de mouton, de bœuf, de jaguar et d'oie. (Lu à l'Académie des sciences le 26 août 1816). *Ann. d. chem. e. d. physique*, Paris, 2:339-72, 1816.
359. CHEVREUL, M. Sur la présence de la cholestérine dans la bile de l'homme. *J. de chim. méd.*, 1:135-36, 1825.
360. CHEVRIER, L. Etudes sur la cholémie post-anesthésique et sur les magens de la modifier. *Bull. et mém. Soc. de chir. de Paris*, 45: 735-77, 1919.
361. CHIKAMORI, S. Über den Einfluss der Gallensäure auf die Glykogenbildung in Geweben. *Okayama-Igakkai-Zasshi*, 44:9-10, 18, 1932.
362. CHIKAMORI, S. Einfluss der Cholsäure auf die Zuckerausscheidung im Harn von kastrierten Kaninchen. *Okayama-Igakkai-Zasshi*, 45: 943, 1933.
363. CHIRAY, M., and FIRMIN, P. La Réserve alcaline et l'acidité ionique de la bile humaine prélevée par tubage duodénal. *Arch. d. mal. de l'app. digestif*, 25:233-42, 1935.
364. CHIRAY, M.; PAVEL, I.; and AMY, P. La Question des biles noires. *Presse méd.*, 39:988-90, 1931.
365. CHIRAY, M., and THIEBAUT, F. Les Fonctions hépato-biliaires. Paris: Masson et Cie, 1930. Pp. 176.
366. CIMINO, S. Il comportamento della cloremia nell'occlusione sperimentale del coledoco. *Ann. ital. di chir.*, 12:451-56, 1933.
367. CLAIRMONT, P. Über Anurie nach Gallensteinoperation. *Mitt. a. d. Grenzgeb. d. Med. u. Surg.*, 22:159, 1910.
368. CLAIRMONT, P., and HABERER v., KREMSHOHENSTEIN, H. Gibt es eine gallige Peritonitis ohne Perforation der Gallenwege? *Wien. klin. Wchnschr.*, 26:891-92, 1913.
369. CLARA, M. Histologische Untersuchungen über die Veränderung der Gallenwege bei künstlich gesteigerter Cholerese durch Dehydrocholsäure (Decholin). *Med. Klin.*, 30:203-5, 1934.
370. CLEMENTI, A., and CONDORELLI, F. Nuove proprietà biologiche dei pigmenti biliari; potere emolitico e potere agglutinante della bilirubina. *Boll. d. Soc. ital. di biol. sper.*, 5:482-85, 1930.
371. CLEMENTI, A., and CONDORELLI, F. Nuove proprietà biologiche dei pigmenti biliari; variazioni del potere emolitico e del potere agglutinante della bilirubina per aggiunta di siero di sangue o di sali biliari. *Boll. d. Soc. ital. di biol. sper.*, 5:486-88, 1930.
372. CLEMENTI, A., and CONDORELLI, F. Nuove proprietà biochimiche dei pigmenti biliari; potere agglutinante della bile sugli stromi degli eritrociti emolizzati. *Boll. d. Soc. ital. di biol. sper.*, 5:748-50, 1930.
373. CLEMENTI, A., and CONDORELLI, F. Nuove proprietà biochimiche dei pigmenti biliari; potere emolitico e potere emoaagglutinante della bilirubina. *Bull. e atti. d. r. Accad. med. di Roma*, 56:240-48, 1930.

374. CLUTE, H. M., and VEAL, J. R. The prediction of hemorrhage in obstructive jaundice by the sedimentation rate. *Ann. Surg.*, **96**:385-93, 1932.
375. COBB, D. B. Affections of the common bile duct associated with jaundice. *Surg., Gynec. Obst.*, **43**:310-16, 1926.
376. COLASANTI, G. La Funzione protettiva del fegato. *Istituto di farmacologia sperimentale*, **3**:xxi-xxxv, 1896.
377. COLASANTI, G. Contributo alla chimica della bile. *Instit. de pharmacol. sperim.*, **4**:1-12, 1899.
378. COLASANTI, G. Beitrag zur Chemie der Galle. *Moleschotts Untersuch. z. Natur. d. Mensch. u. d. Thiere. E. Roth. Giessen*, **16**:284-93, 1899.
379. COLBECK, J. C. Haemorrhage in jaundiced patients. *Guy's Hosp. Gaz.*, **46**:138-44, 157-65, 1932.
380. COLE, W. H. Congenital malformations of the intestines and bile tract in infancy and in childhood. *Arch. Surg.*, **23**:820-47, 1931.
381. COLP, R., and DOUBILET, H. Differential analysis of bile acids in human gallbladder bile. *Arch. Surg.*, **33**:913-25, 1936.
382. COOPER, E. F. Toxicity of alcoholic extracts of ox-bile when fed to white rats. *Am. J. Physiol.*, **65**:363-67, 1923.
383. COPE, Z. Extravasation of bile. (Hunterian Lecture.) *Brit. J. Surg.*, **138**:120-29, 1925.
384. COPEMAN, S. M., and WINSTON, W. B. Observations on human bile obtained from a case of biliary fistula. *J. Physiol.*, **10**:213-31, 1889.
385. COQUELET, O. Le Réaction furfurol sulfurique (Pettenkoefers). *Comp. rend. Soc. de biol.*, **97**:747-48, 749-50, 1815-18, 1927.
386. COQUELET, O. Bile et coagulation du sang. *Compt. rend. Soc. de biol.*, **109**:977-79, 1932.
387. COQUELET, O. Action des sels biliaires sur le système nerveux central. *Compt. rend. Soc. de biol.*, **117**:114-17, 1934.
388. COQUELET, O. Action des sels biliaires sur les nerfs périphériques. *Compt. rend. Soc. de biol.*, **117**:118-20, 1934.
389. CORBEL, P. Le Pouls dans les divers ictères (inconstance de la bradycardie, ses raisons étiologiques et sa valeur séméiologique). *Lyon*, 1905.
390. CORNAC, M. Essai sur la jaunisse ou l'ictère. *Paris*, 1809.
391. CORNEJO-SARAVIA, E.; MAZZOCCO, P.; and ROYER, M. Los Acidos biliares de la sangre después de la hepatectomía. *Rev. Soc. Argentina biol.*, **5**:110-13, 1929.
392. CORNELI, W. Bemerkungen über das sogenannte Vitamin A. *Ztschr. f. physiol. Chem.*, **191**:86-88, 1930.
393. CORPER, H. J.; COHN, M. L.; and HOPER, V. J. Sodium taurocholate and the virulence of human tubercle bacilli. *J. Lab. & Clin. Med.*, **19**:1179-83, 1934.

394. CORTESE, F., and BASHOUR, J. T. Synthesis of conjugated bile acids. Sodium taurocholate and sodium taurodesoxycholate. *J. Biol. Chem.*, **119**:177-83, 1937.
395. COSTINESCU, C. Eine neue Methode zur Behandlung der Syphilis mit in Gallensaeuren geloesten grossen Dosen von Arspfenamin. Diss. Bucharest, 1930.
396. Co TUI, F. W. The combined effects of bile salts and oleic acid on choleresis. *J. Lab. & Clin. Med.*, **19**:56-71, 1934.
397. COUNSELLER, V. S., and McINDOE, A. H. Dilatation of the bile ducts (hydrohepatosis). *Surg. Gynec. Obst.*, **43**:29-40, 1926.
398. COUNSELLER, V. S. Certain effects of obstruction of the bile ducts. *Ann. Surg.*, **87**:210-30, 1928.
399. COURTOIS, G. L'Action de la bile de bœuf sur le virus vaccinal. *Compt. rend. Soc. de biol.*, **119**:551-52, 1935.
400. COURVOISIER, L. G. Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege. Leipzig: Vogel, 1850. *Deutsche Ztschr. f. Chir.*, **32**:598-604, 1891.
401. COUVELAIRE, A.; LEMIERRE, A.; and LENORMANT, C. Bile. In *Pratique médico-chirurgicale* (3d ed.), 1931.
402. COXE, J. R. The writings of Hippocrates and Galen. Philadelphia: Lindsay & Blakiston, 1846.
403. CRANMER, W., and LUDFORD, R. J. On the cellular mechanism of bile secretion and its relation to the Golgi apparatus of the liver cell. *J. Physiol.*, **62**:74, 1926.
404. CRILE, G. W. Bulletin of the Chicago Medical Society, 1927, p. 26.
405. CROFTAN, A. C. Zur Kenntnis des intermediären Kreislaufs der Gallensäuren. *Pflüger's Arch. f. d. ges. Physiol.*, **90**:635-39, 1902.
406. CROFTAN, A. C. The bile acids as a remedy. *New York M. J.*, **83**:810-12, 1906.
407. CROISSANT, R. Recherches sur la dissociation de la sécrétion biliaire. Paris, 1913.
408. CULLIGAN, J. Gradual decompression of biliary system; mechanical factor in post-operative hemorrhage and hepatic insufficiency in jaundiced patients. *Minnesota Med.*, **16**:15-19, 1933.
409. CUMMINS, S. L. Anti-bactericidal action of bile salts. *J. Hyg.*, **11**:373-80, 1911.
410. CUMSTAN, C. G. Biliary peritonitides. *Internat. Clin. Phila.*, 1921, pp. 60-65.
411. CUMSTAN, C. G. Icterus gravis. *New York M. J.*, **113**:200-201, 1921.
412. CUNY, LOUIS. La Dosage des sels biliaries dans la bile et la liquide duodénal. Paris: Masson et Cie, 1930. Pp. 201.
413. CUSHNEY, A. R. Pharmacology and therapeutics, p. 709. Philadelphia: Lea Brothers & Co., 1906.

414. CUTTEN, C.; EMERSON, E. E.; and WOODRUFF, W. The icterus index. Spectrophotometric and quantitative studies. *Arch. int. Med.*, 41:428-44, 1928.
415. DA COSTA, J. C. *Modern surgery* (9th ed.), pp. 1016 and 1024. Philadelphia: W. B. Saunders Co., 1925.
416. DALLA TORRE, G., and DUSSO, R. Le Modificazioni elettrocardiografiche nell'ittero da stasi. *Ricerche cliniche e sperimentali. Cuore e circolax.*, 20:194-204, 1936.
417. DALSACE, J. Les Biles noires. *Progrès méd.*, 1932, pp. 1741-42.
418. DALTON, J. C. On the constitution and physiology of the bile. *Am. J. Med. Sc.*, 60 (N.S. 34):305-23, 1857.
419. DAM, H., SCHOENHEYDER, F.; and TAGE-HANSEN, E. Studies on the mode of action of vitamin K. *Biochem. J.*, 30:1075-79, 1936.
420. DANIELOPOLU, D.; PROCA, G. G.; and BRAUNER, R. Über die Rolle der Leber in der Regulierung des Tonus des vegetativen Nervensystems und über den Entstehungsmechanismus der ikterischen Bradykardie. *Wien. klin. Wchnschr.*, 43:1432-34, 1930.
421. DANILEWSKY, B. De l'influence de la lecithine sur l'activité du cœur. *J. de physiol. et de pathol. gén.*, 9:909-24, 1907.
422. DANILEWSKY, B. Über die Wirkung des Cholesterins auf's Froschherz. *Pflügers Arch. f. d. ges. Physiol.*, 120:181-92, 1907.
423. DA-RIN, O., and BACCHETTA, M. Contributo clinico allo studio della mucino-albuminocolia nelle affezioni epatiche. *Fisiol. e med.*, 4:7-40, 1933.
424. DASGUPTA, SURENDRANATH. *A history of Indian philosophy*, 2:325-37. London: Cambridge University Press, 1932.
425. DASTRE, A. Recherches sur la bile. *Arch. de physiol. norm. et path.*, 2:315-30, 1890.
426. DASTRE, A. Bile. In *Richet Dictionnaire de physiologie*, 2:148-20, 1897.
427. DASTRE, A. Observations sur l'historique de quelques points de l'étude de la bile. *Compt. rend. Soc. de biol.*, 5:144-46, 1898.
428. DAUGUET, A. Etude sur la physiologie de la bile; conséquences thérapeutiques. Paris, 1907.
429. DAVID, V. C., and LORING, M. Experimental peritonitis. *Arch. Surg.*, 26:1103-10, 1933.
430. DAVIDSON, L. R. Preoperative and postoperative care of biliary tract and liver cases. *S. Clin. No. Amer.*, 12:477-81, 1932.
431. DAVIES, D. T., and DODDS, E. C. A study of the properties of pure bilirubin and its behaviour towards the van den Berg reactions. *Brit. J. Exper. Path.*, 8:316-25, 1927.
432. DAVIS, G. E., and SHEARD, C. The spectrophotometric determination of hemoglobin. *Arch. Int. Med.*, 40:226-36, 1927.

433. DAVIS, J. E. In vitro hydrolysis of fats by lipase and bile salts. *Proc. Soc. Exper. Biol. & Med.*, 34:72-75, 1936.
434. DAVIS, L. Reflux of duodenal contents through the common bile duct. *New England J. Med.*, 200:313-18, 1929.
435. DE BRUIN, J. Bijdrage tot de leer der geelzucht met het oog op de vergiftige werking der bilirubine. Dissertation, Amsterdam, 1889. *Rev. de méd.*, Paris, 10:600-605, 1890.
436. DE BRUIN, J. Über die giftige Wirkung des Bilirubins bei der Gelbsucht. *Zentralbl. f. klin. Med.*, 11:491-92, 1890.
437. D'ERRICO, G. Wirkung der Galle und der Gallensäuren Salze auf den Tonus und die automatischen Bewegungen des Darmrohrs. *Ztschr. f. Biol.*, 54:286-98, 1910.
438. DEHIO, K. Über Bradycardie und die Wirkung des Atropin auf das gesunde und kranke menschliche Herz. *Petersburger med. Wchnschr.*, 9:1-5, 1892. *Deutsches Arch. f. klin. Med.*, 52:74, 1893.
439. DÉIDIER, A. In Bianchi Hist. hepatica, Part III, p. 804. Genevae, 1725. *Journal savans*, 1722. *Phil. Trans.*, No. 370.
440. DÉIDIER, A. De bile peste emortuorum experimenta. *Halleri Biblioth. Anat.*, 1:808.
441. DEITIER, ANTONIUS. Expériences sur la bile et les cadavres des pestifères accompagnées des lettres du dit Nr. Deidier. Zurich, 1722. Pp. 76.
442. DE L'ARBRE. Über die Verbindung einzelner Alkaloide mit Gallensäuren. Dissertation. Dorpat, 1871.
443. DE LAVERGNE, V.; KISSEL, P.; SIMONIN, J.; and LÉVY, J. Bacillus perfringens et bile. *Compt. rend Soc. de biol.*, 112:1366-68, 1933.
444. DE LAVERGNE, V., and KISSEL, P. Etude des conditions physico-chémiques de la formation des calculs biliaires. *Ann. de méd.*, 37:105-16, 1935.
445. DE LAVERGNE, V., and KISSEL, P. Etude critique des théories pathogéniques de la lithiase biliaire. *Ann. de méd.*, 37:117-30, 1935.
446. DELBET, P., and BEAUVY, A. Du magnésium et du calcium dans la bile. *Bull. Acad. de méd. Paris*, 105:987-95, 1931.
447. DELORE, M. P. Sur l'influence de la quantité des boissons sur la densité de la bile. *Lyon méd.*, 150:604-6, 1932.
448. DEMARÇAY, H. De la nature de la bile. *Ann. de chem. et de physique*, 67:177-203, 1838.
449. DEPLAS, B., and DALSACE. Les Biles noires. *Presse méd.*, 38:937-39, 1930.
450. DESPLAS, B., and DALSACE, J. Bile noire et lithiase biliaire. *Presse méd.*, 40:523-25, 1932.
451. DESJARDINS, A. Etude sur les pancréatites. Thèse de Paris, Steinhil, 1905. Pp. 208.

452. DEULOFEU, V. Die Gallensäure der Galle von Schlangen. *Ztschr. f. physiol. Chem.*, **229**:157-58, 1934.
453. DÉVÉ, F. De l'action de la bile sur les germes hydatiques. *Comp. rend. Soc. de biol.*, **55**:75-77, 1903.
454. DEYEUX, N. Considérations chimiques et médicales sur le sang des ictériques. Paris, 1804.
455. DHÉRE, C. Sur la fluorescence rouge que présentent en lumière ultraviolette, certains dérivés de la bilirubine. *Compt. rend. Soc. de biol.*, **103**:371-74, 1930.
456. DIAMOND, J. S. The value of routine estimation of blood bilirubin. *Am. J. M. Sc.*, **176**:321, 1928.
457. DIEMERBROECK, IJSBRAND VAN. De atrâ bile. Leipzig, 1740.
458. DIETERICH, H. Die porotische Malacie nach Gallenfisteln. *Beitr. z. klin. Chir.*, **134**:530-53, 1925.
459. DIETRICH, W. Resorption von Tetanusgift durch den Darm. *Klin. Wchnschr.*, **1**:1160-61, 1922.
460. DIJKSTRA, O. H. [Jaundice from rupture of choledochus in nursing.] *Maandschr. v. kindergeneesk.*, **1**:409-14, 1932.
461. DILL, L. V. Effect of obstructive jaundice on blood platelets of rabbit. *J. Lab. & Clin. Med.*, **21**:899-905, 1936.
462. DIMITRIJEVIĆ-SPETH, V. Die Abschwächung des Flecktyphusvirus durch Gallebehandlung und Immunisierungsversuche mit gallegeschwächtem Hirnvirus. *Zentralbl. f. Bakt.*, **134**:67-70, 1935.
463. DIPHILUS. *Frag.* 2.
464. DOGIEL, J. Über das Vorkommen flüchtiger Fettsäuren in der Galle. *Jr. f. prak. Chemie*, **101**:298-301, 1867.
465. DOKHMANN, A. [Effect on the bile raising or reducing temperature of body.] *Med. Obozr., Mosk.*, **26**:162-74, 1886.
466. DOLJANSKI, L., and KOCH, O. Der Blutfarbstoff und die lebende Zelle. *Virchows Arch. f. path. Anat.*, **291**:378-89, 390-96, 397-400, 1933.
467. DONATI, D., and CAVAZZA, F. Sulla produzione sperimentale dell'ulcera gastrica e duodenale in seguito a derivazione totale della bile e studio della alterazioni degli organi interni. *Arch. ital. di anat. e istol. pat.*, **5**:873-90, 1934.
468. DONATI, A., and SATTA, G. Influence de quelques substances protéiques sur l'hémolyse déterminée par le glycocholate et par l'oléate sodiques. *Arch. ital. de biol.*, **50**:1-7, 1908.
469. DOSTAL, L. E., and ANDREWS, E. Sixteen months survival with complete obstruction of bile ducts in dog. *Proc. Soc. Exper. Biol. & Med.*, **29**:547-48, 1932.
470. DOSTAL, L. E., and ANDREWS, E. Effect of diet on the bile-salt-cholesterol ratio. *Arch. Surg.*, **26**:258-71, 1933.

471. DOUBILET, H. Differential quantitative analysis of bile acids in bile and in duodenal drainage. *Proc. Soc. Exper. Biol. & Med.*, **34**:86-88, 1936.
472. DOUBILET, H., and COLP, R. Differential analysis of bile acids in human bile from fistulas. *Arch. Surg.*, **34**:151-53, 1937.
473. DOUMER, E. L'action du taurocholate de soude sur la tension de soude sur la tension superficielle de l'eau. *Compt. rend. Soc. de biol.*, **85**:1138-39, 1921.
474. DOUMER, E. Recherches pour servir à l'étude de la cholalurie. Thèse de Paris, 1922.
475. DOURMASHKIN, R. L. A urohepatic syndrome. *J.A.M.A.*, **90**:908-10, 1928.
476. DOUSTE-BLAZY, S. De la forme rénale de l'ictère grave. Thèse de Paris, 1906-7.
477. DOWNIE, A. W.; STENT, L.; and WHITE, S. M. Bile solubility of pneumococcus; chemical structure of various bile salts. *Brit. J. Exper. Path.*, **12**:1-8, 1931.
478. DOWNS, A. W. The influence of internal secretions on blood pressure and the formation of bile. *Am. J. Physiol.*, **52**:498-507, 1920.
479. DOWNS, A. W., and EDDY, N. B. The influence of internal secretions on the formation of bile. *Am. J. Physiol.*, **48**:192-98, 1919.
480. DOYON, M. Action de la bile sur la coagulabilité du sang. *J. de physiol. et de path. gén.*, **12**:197-201, 1910.
481. DOYON, M., and BILLET, J. Rapport entre l'incoagulabilité du sang et les lésions hépatiques dans l'intoxication subaiguë par le chloroforme. *Compt. Rend. Soc. de biol.*, **58**:852, 1905.
482. DOYON, M., and DUFOURT, E. Recherches sur la teneur de la bile en cholestérine. *Compt. rend. Soc. de biol.*, **3**:487-89, 1896.
483. DOYON, M., and GAUTIER, C. Action de la bile sur la coagulabilité du sang par l'intermédiaire du foie. *Compt. rend. Soc. de biol.*, **77**:428-29, 1909.
484. DOYON, M., and GAUTIER, C. Expérience concernant le rôle du foie dans la coagulation du sang. *Compt. rend. Soc. de biol.*, **66**:442, 1909.
485. DOYON, M., and GAUTIER, C. Action de la bile sur la coagulation du sang expériences sur le lapin. *Compt. rend. Soc. de biol.*, **66**:593-94, 1909.
486. DOYON, M., and GAUTIER, C. Nocivité comparée de la bile, suivant que le poison est injecté dans une veine mésentérique ou dans la saphène. *Compt. rend. Soc. de biol.*, **68**:210, 1910.
487. DOYON, M.; MOREL, A.; and KAREFF, N. Teneur en fibrinogène du sang rendu incoagulable par l'atropine. *Compt. rend. Soc. de biol.*, **58**:428, 1905.

488. DRAGSTEDT, L. R., and SPURRIER, B. Effect of diversion of bile into vena cava and portal vein in dogs. *Proc. Soc. Exper. Biol. & Med.*, 26:303, 1928.
489. DRAGSTEDT, L., and WOODBURY, R. A. The relation of bile to the secretion of pancreatic juice. *Am. J. Physiol.*, 107:584-88, 1934.
490. DRENNAN, J. G. A bacteriologic study of the fluid contents of 100 gallbladders removed at operation. *Ann. Surg.*, 76:482, 1922.
491. DREYFUS-BRISAC, L. De l'ictère hemaphéique principalement au point devue clinique. Thèse de Paris, 1878. Pp. 101.
492. DRURY, D. R. Conditions influencing the calcium content of the bile. *J. Exper. Med.*, 40:797-815, 1924.
493. DRURY, D. R., and ROUS, P. Suppression of bile as a result of impairment of liver function. *J. Exper. Med.*, 41:611, 1925.
494. DUBOS, R. J. Mechanism of the lysis of pneumococci by freezing and thawing, bile, and other agents. *J. Exper. Med.*, 66:101-12, 1937.
495. DUCHESNE, J. Forme rénale de l'ictère acholurique simple. Paris, 1901.
496. DUDGEON, L. S. Action of bile and bile salts with or without calcium salts on red corpuscles. *J. Hyg.*, 16:240-48, 1918.
497. DUFOUR, E. Du rythme couplé du cœur avec pouls bigéminé au cours de l'ictère. *Gazette hebdomadaire de méd. et de chir.*, 86: 1022, 1901.
498. DÜKER, W. Dehydrocholsaures Natrium. *Deutsche. med. Wchnschr.*, 52:1919, 1926.
499. DUMITRESCO-MANTE and CIORAPICU, S. L'Action du glycocholate et du taurocholate de soude en solution dans le liquide de Ringer-Locke sur le cœur isolé de la grenouille. Absence d'une action bradycardisante. *Compt. rend. Soc. de biol.*, 101:225-26, 311-12, 1929.
500. DUMITRESCO-MANTE and HAGIESCO. L'Action des injections de sels biliaires sur le rythme du pouls chez le singe normal. *Soc. de Biol. réunion roumaine, séance du 17 Mai 1928.*
501. DUMITRESCO-MANTE, HAGIESCO, MAXIMIN, and PETRESCO. Sur le mécanisme de la bradycardie ictérique. *Bull. de l'Acad de méd. de Paris. Séance du 24 Juille 1928* No. 30, p. 881.
502. DUMITRESCO-MANTE; HAGIESCO, D.; MAXIM, M.; and PETRESCO, C. Nouvelles recherches sur la bradycardie ictérique. *Presse méd.*, 37: 34-36, 1929.
503. DUNGLISON, R. J. *Human physiology*, 2:528. Philadelphia: Carey & Lea, 1932.
504. DÜTTMANN, G. Die Veränderung des Säure-Basengleichgewichtes nach Gallen fisteln und ihre Bedeutung bei der Entstehung der sog. parotischen Malacie. *Beitr. z. klin. Chir.*, 139:720-29, 1927.

505. EBSTEIN, W. Zur Etymologie des Wortes Gelbsucht und der dafür gebräuchlichen Synonyme. Deutsche med. Wchnschr., 29:103-5, 1903.
506. ECKHARD, C. Über den Einfluss der Galle auf die peristaltischen Bewegungen des Dünndarmes. Zentralbl. f. Physiol., 13:49-54, 1899.
507. EDINGTON, G. H. The bile-salts in their relation to the secretion of urea. J. Anat. & Physiol., 30:215-37, 1895-96.
508. EDMUNDS, A. The effect of salts of potassium, ammonium and bile salts upon blood pressure. Brit. M. J., 1:57-59, 1905.
509. EDWARDS, H. M. Leçons sur la physiologie et l'anatomie comparée de l'homme et des animaux, 7:94. Paris: V. Masson, 1857-79.
510. EHRHARDT, O. Über Gallenresorption und Giftigkeit der Galle im Peritoneum. Arch. f. klin. Chir., 64:314-38, 1901.
511. ERMAN, A., and KREBS, F. Aus den Papyrus der Königlichen Museen. Handbücher der Königlichen Museen zu Berlin, p. 74. Berlin: W. Spemann, 1899.
512. EIBEL, H. Über die gerinnungshemmende Wirkung der Galle in vitro. Biochem. Ztschr., 256:398-405, 1932.
513. EIBEL, H. Über die gerinnungshemmende Wirkung der Galle in vitro. Biochem. Ztschr., 265:36-40, 1933.
514. EILBOTT, W. Funktionsprüfung der Leber mittels Bilirubinbelastung. Ztschr. f. klin. Med., 106:529-60, 1927.
515. EITEL, H. Ein Beitrag zum Wesen des Toluylendiaminikterus. Beitr. z. Path. Anat. u. z. allg. Pathol., 79:700-712, 1928.
516. ELLIOTT, T. R., and WALSHE, F. M. R. The Babinski or extensor form of plantar response in toxic states apart from organic disease of the pyramidal tract system. Lancet, 1:65-68, 1925.
517. ELLIS, J. C., and DRAGSTEDT, L. R. Liver autolysis in vivo. Arch. Surg., 20:8, 1930.
518. ELMAN, R., and HARTMANN, A. F. Spontaneous peptic ulcers of duodenum after continued loss of total pancreatic juice. Arch. Surg., 23:1030-40, 1931.
519. ELMAN, R., and McMASTER, P. D. Quantitative determination of urobilin. J. Exper. Med., 41:503-12, 1925.
520. ELMAN, R., and McMASTER, P. D. Urobilin and damaged liver. J. Exper. Med., 42:99, 1925.
521. ELMAN, R., and McMASTER, P. D. The physiological variations in resistance to bile flow in the intestines. J. Exper. Med., 44:No. 2, 151-71, 1926.
522. ELMAN, R., and TAUSSIG, J. B. Cholesterol content of "white bile" from various sources, including contents of "hydrops" of gallbladder. Proc. Soc. Exper. Biol. & Med., 28:1070-71, 1931.

523. ELMER, A. W., and LUCZYNSKI, Z. L'Excrétion d'iode par la bile, à jeûn et après le repas. *Compt. rend. Soc. de biol.*, 114:1340-42, 1933.
524. ELMER, A. W., and LUCZYNSKI, Z. Sur l'élimination par la bile de la thyroxine administrée par voie entérale. *Compt. rend. Soc. de biol.*, 115:647, 1934.
525. ELTON, N. W. Physiology, correlations, and technic of van den Bergh reaction, icterus index, and quantitative serum bilirubin. *J. Lab. & Clin. Med.*, 17:1-13, 1931.
526. ELTON, N. W. Postoperative latent jaundice. *Surg. Gynec. Obst.*, 53:657-66, 1931.
527. ELTON, N. W. Bilirubin concentrations in the human gallbladder. *Am. J. Clin. Path.*, 6:81-90, 1936.
528. ELTON, N. W., and DEUTSCH, E. Concentration and precipitation of bilirubin in the gallbladder and bile ducts. *Arch. Path.*, 15:818-27, 1933.
529. EMERSON, W. C. Distribution of calcium in jaundiced and acholic dogs. *J. Lab. & Clin. Med.*, 14:122-31, 1928.
530. EMERSON, W. C. Toxic constituent of bile. *J. Lab. & Clin. Med.*, 14:635-43, 1929.
531. EMERSON, W. C. The effect of calcium chloride upon the toxicity of bile. *J. Lab. & Clin. Med.*, 14:714-18, 1929.
532. ENGELSTAD, R. B. Kalkgalle. *Norsk magasin for laegevidenskapen*, Oslo, 96:407-11, 1935.
533. ENGLER, L. Zur Therapie der Gallenwegerkrankungen. *Zentralbl. f. inn. Med.*, 51:337, 1930.
- 534.*EPPINGER, H. Der Ikterus. *Ergebn. d. inn. Med. u. Kinderh.*, 1: 107-56, 1908.
535. EPPINGER, H. Die Pathogenese des Ikterus. *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 34:13-39, 1922.
536. EPPINGER, H., and ELEK, L. Gallenabsonderung und Gallenableitung. *Handbuch der normalen und pathologischen Physiologie*, 3:1264-91, 1929.
537. EPPINGER, H., and WALZEL, P. Die Krankheiten der Leber mit Einschluss der hepatolienalen Affektionen. *Diagnostische und therapeutische Irrtümer und deren Verhütung innere Medizin*. Leipzig, 1926. Pp. 134.
538. EPSTEIN, E. Z. Cholesterol of blood plasma in hepatic and biliary diseases. *Arch. Int. Med.*, 50:203-23, 1932.
539. ERB, K. H., and BARTH, F. Tryptisches Ferment im Inhalt extirpierter Gallenblasen, zugleich ein Beitrag zur Bakteriologie der Galle. *Beitr. z. klin. Chir.*, 134:507-26, 1925.

540. ERBE, J. L. J. De bile morbisque biliosis. Diss., Erlangae, 1793.
541. ERBSEN, H. Untersuchungen zur Funktion der extrahepatischen Gallenwege. *Ztschr. f. d. ges. exper. Med.*, 61:316-22, 1928.
542. ERHART, F. Kasuistischer Beitrag zur Anwendung des Decholins. *Med. Klin.*, 30:678-79, 1934.
543. ERNST, C. Über die Fäulnisprodukte der Galle und deren Einfluss auf die Darmfaulniss. Strassburg, 1893. *Ztschr. f. physiol. Chem.*, 16:205-19, 1891-92.
544. ERNST, Z. Untersuchung über extrahepatogene Gallenfarbstoffbildung an überlebenden Organen. Untersuchungen an überlebender Milz, Niere und Lunge. *Biochem. Ztschr.*, 157:30-38, 1925.
545. ERNST, Z., and HALLAY, E. Zur Frage der Bilirubinbildung durch Fermente und Bakterien. *Ztschr. f. d. ges. exper. Med.*, 78:325-36, 1931.
546. ERNST, Z., and SZAPPANYOS, B. Untersuchungen über extrahepatogene Gallenfarbstoffbildung an überlebenden Organen. Untersuchungen an überlebender Milz. *Biochem. Ztschr.*, 157:1-29, 1925.
547. ESCUDERO, P., and ITHURAT, E. F. La Resistencia globular y la bilirrubinemia en las diversas formas de eritrocitosis. *Rev. Asoc. méd. argent.*, 39:365-73, 1926.
548. EUFINGER, H., and BADER, C. W. Die Bedeutung der H. v. d. Bergh'schen Probe in der Schwangerschaft insbesondere bei Toxikosen. *Zentralbl. f. Gynäk.*, 50:514-16, 1926.
549. EUFINGER, H.; WIESBADER, H.; and FOCSANEANU, L. Die Gallensalzresistenz der Erythrocyten in der Gestations-periode. *Arch. f. Gynäk.*, 140:21-26, 1930.
550. EURIPIDES. *Thuc.* 2. 49. *Electra* 828.
551. EUSTERMAN, G. B. The nature, cause and incidence of error in the diagnosis of conditions underlying jaundice. *Proc. Staff Meet. Mayo Clinic*, Aug. 31, 1932, pp. 504-5.
552. EWALD, C. A. Gelbsucht. In *Real-Encyclopädie der gesamten Heilkunde* by Eulenburg, 8:208-18, Wien and Leipzig, 1886.
553. FABRIS, U. La Picmentazione verde delle ossa nell'itterizia intensa secondaria a ferita del pancreas. *Gazz. internaz. med.-chir.*, 40:343-47, 1932.
554. FAITHHORN, J. Facts and observations on liver complaints and bilious disorders in general; biliary secretion. Philadelphia: Hickman & Hazzard, 1822. Pp. 188.
555. FALTITSCHEK, J. Zur Pathogenese des Icterus catarrhalis. *Ztschr. f. klin. Med.*, 128:480-90, 1935.
556. FALUDI, F. Kolloidstudien über Gallen- und Nierensekretion. *Ztschr. f. d. ges. exper. Med.*, 6:121-26, 127-32, 133-38, 139-42, 143-49, 1928.

557. FARIOLI, A. L'Azione in vitro della bile fresca, della bile secca e del taurocolato sodico sullo streptococco dell'eresipela. *Pediatria*, 42: 611-19, 1934.
558. FASCE, L. La Bile e l'acido glicocolico nel sangue dei cani e dei conigli. *Gaz. clin. d. ospedale civico di Palermo*, 1869.
559. FASIANI, G. M. Expériences préliminaires sur les rapports entre le contenu de cholestérine dans le sang et dans la bile. *Arch. ital. de biol.*, 63:136-43, 1915.
560. FAY, O. J. Injuries to the biliary passages. In A. J. Ochsner's *Surgical diagnosis and treatment*, 4:736-38. Philadelphia: Lea & Febiger, 1922.
561. FEIGL, J., and QUARNER, E. Bilirubinämie in ihren psychologisch-chemischen Beziehungen mit besonderer Berücksichtigung der diagnostischen Bedeutung. *Ztschr. f. d. ges. exper. Med.*, 9:153, 250, 1919.
562. FELDMAN, W. M., and LAWSON, M. A. Case of congenital occlusion of the common hepatic duct in a twin baby with an indirect v. d. Bergh reaction. *Lancet*, 2:113, 1924.
563. FELLINGER, K., and POPPER, H. Über latenten Ikterus nach Narkosen. *Arch. f. klin. Chir.*, 172:575-90, 1932.
564. FELTZ, V., and RITTER, E. De l'action des divers principes de la bile sur l'organisme. *J. de l'anat. et de la physiol.*, 6:315-18, 1870.
565. FELTZ, V., and RITTER, E. Action de la bile et de ses principes introduits dans l'organisme. *J. de l'anat. et de la physiol.*, 10:391-409, 1874.
566. FELTZ, V., and RITTER, E. Action des sels biliaries sur l'économie. *J. de l'anat. et de la physiol.*, 10:561-88, 1874.
567. FELTZ, V., and RITTER, E. Etudes expérimentales sur l'influence des injections de bile sur l'organisme. *Compt. rend. Soc. de biol.*, 78: 1444-46, 1874.
568. FELTZ, V., and RITTER, E. Action sur l'économie des dérivés des acides biliaries des matières colorantes et de la cholestérine de la bile. *J. de l'anat. et de la physiol.*, 11:147-71, 1875.
569. FELTZ, V., and RITTER, E. De la ligature du canal cholédoque, et parallèle entre les données expérimentales et les données cliniques. *J. de l'anat. et de la physiol.*, 11:405-31, 1875.
570. FELTZ, V., and RITTER, E. De l'apparition des sels biliaries dans le sang et les urines. *J. de l'anat. et de la physiol.*, 12:91-110, 1876.
571. FELTZ, V., and RITTER, E. De l'action des sels biliaries sur le pouls, la tension, la respiration et la température. *J. de l'anat. et de la physiol.*, 12:270-87, 1876.
572. FELTZ, V., and RITTER, E. De l'action de la digitale comparée à celle des sels biliaries sur le pouls, la tension artérielle, la respiration et la température. *Compt. rend. Soc. de biol.*, 82:1343-44, 1876.

573. FERNHOLTZ, E. Die Isolierung der 3-oxy-6-keto-allocholansäure aus Schweinegalle. *Ztschr. f. physiol. Chem.*, 232:202-5, 1935.
574. FIESSINGER, N., and GAJDOS, A. L'Evolution de la bilirubinurie et et de la cholalurie après l'écrasement de la rate. *Compt. rend. Soc. de biol.*, 109:1078-79, 1932.
575. FIESSINGER, N., and ROUNDOVSKA, L. La Cirrhose biliaire expérimentale. *Arch. de méd. expér. et d'anat. path.*, 26:18-50, 1914-15.
576. FIESSINGER, N., and WALTER, H. L'Exploration fonctionnelle du foie et l'insuffisance hépatique. Paris: Masson et Cie, 1925. Pp. 388.
577. FIESSINGER, N., and WALTER, H. La Bilirubimétrie plasmatique. Son but, sa technique, ses enseignements. *Nutrition*, 1:225-60, 1931. Paris: Doin.
578. FIFIELD, L. R. Perforation and rupture of the gallbladder. *Brit. M. J.*, 2:635-70, 1926.
579. FIGURELLI, G. Sugli effetti della bile pervenuta in cavità peritoneale e sulla interpretazione di essi. *Ricerche sperimentali. Ann. ital. di chir.*, 11:641-60, 1932.
580. FINKELSTEIN, R., and LIPSCHUTZ, E. W. A comparative study of the choleretic effect of bile salts and oleic acid and bile salts. *Ann. Int. Med.*, 6:1465-73, 1933.
581. FINSTERER, H. Über Leberverletzungen. *Deutsche Ztschr. f. Chir.*, 118:1, 1913.
582. FINSTERER, H. Erfolge und Misserfolge bei Gallenstemoperationen. *Med. Klin.*, 22:1874, 1914-17, 1926.
583. FISCHER, F. Über die Wirkung der Galle auf Typhus- und Milzbrandbacillen. Bonn, 1894.
584. FISCHER, H. Zur Kenntnis der Gallenfarbstoffe. *Ztschr. f. physiol. Chem.*, 73:204-39, 1911.
585. FISCHER, H. Zur Kenntnis des Gallenfarbstoffs. *Ztschr. f. physiol. Chem.*, 89:262, 1914.
586. FISCHER, H. Über Blut- und Gallenfarbstoff. *Ergebn. d. Physiol.*, 15:185, 1916.
587. FISCHER, H., and ADLER, E. Synthese der Bilirubin- und Xanthobilirubinsäure und ihrer Isomeren, sowie Synthese von Tripyrranen und bilirubinoiden Farbstoffen. *Ztschr. f. physiol. Chem.*, 197:237-80, 1931.
588. FISCHER, H., and EISMAYER, K. Experimentelle Studien über die Konstitution des Blut- und Gallenfarbstoffs. *Berl. d. deutsch. chem. Gesellsch.*, 47:2019-27, 1914.
589. FISCHER, H., and LINDNER, F. Zur Kenntnis des Gallenfarbstoffs. *Ztschr. f. physiol. Chem.*, 161:1-17, 1926.
590. FISCHLER, F. Das Urobilin und seine klinische Bedeutung. *Inaug. Diss., Heidelberg*, 1906. *München. med. Wehnschr.*, 53:1783, 1906.

591. FISCHLER, F. *Physiologie und Pathologie der Leber*. Berlin: Julius Springer, 1925. Pp. 310.
592. FITZ, R., and ALDRICH, M. Clinical observations on certain constituents of bile. *J.A.M.A.*, **79**:2129-32, 1922.
593. FLEBBE, J. Über angeborene Obliteration der grossen Gallenwege. Wiesbaden, 1907.
594. FLEISCHL (v. MARKOW), E. Von der Lymphe und den Lymphgefässen der Leber. *Arb. a. d. physiol. Anstalt. zu Leipzig*, **9**:24-37, 1875.
595. FLEXNER, S. The constituent of the bile causing pancreatitis and the effect of colloids upon its action. *J. Exper. Med.*, **8**:167-77, 1906.
596. FLEYS, J. P. Contribution à l'étude des ruptures spontanées des voies biliaires dans le péritoine. Paris, 1899.
597. FLINT, A., JR. Experimental researches into a new excretory function of the liver (cholesterine). *Am. J. M. Sc.*, **44**:305-65, 1862.
598. FLINT, A., JR. Recherches expérimentales sur une nouvelle fonction du foie. Paris, 1868.
599. FLORENTIN, P. Formation des pigments biliaires aux dépens du noyau de la cellule hépatique chez l'embryon humain. *Compt. rend. Soc. de biol.*, **88**:769, 1923.
600. FODERA, F. A., and ZUCCALA, M. Contributi allo studio della bile e della secrezione biliare. *Boll. d. Soc. ital. di biol. sper.*, **3**:1081-88, 1928.
601. FODOR, A. Die Gallensäuren. *Biochem. Handlexikon*, hrsg. v. E. Abderhalden, **8**:494-500. Berlin: J. Springer, 1914.
602. FODOR, J. Über gallige Peritonitis. *Beitr. z. klin. Chir.*, **158**:270-82, 1933.
603. FONTANA, E. Influenza dei sali biliari sulla vitalità de bacillo tifico, del colibacillo, del diplococco, della streptococco. Tommasi, Napoli, **3**:415-18, 1908.
604. FOOTE, F. S., and CARR, J. L. Obstructive jaundice. *Surg. Gynec. Obst.*, **63**:570-75, 1936.
605. FORD, W. W. Obstructive biliary cirrhosis. *Am. J. M. Sc.*, **121**:60, 1901.
606. FORNET, W. Über die Bakterizidie der Galle. *Arch. f. Hyg.*, **60**:134-43, 1907.
607. FORSGREN, E. On the relationship between the formation of bile and glycogen in the liver of rabbit. *Skandin. Arch. f. Physiol.*, **53**:137-51, 1928.
608. FORSGREN, E. 24-Stunden-Variationen der Gallensekretion. *Skandin. Arch. f. Physiol.*, **59**:217-25, 1930.
609. FORSGREN, E. Über die Beziehungen zwischen Schlaf und Leberfunktion. *Skandin. Arch. f. Physiol.*, **60**:299-310, 1930.

610. FORSGREN, E. Über die Rhythmik der Leberfunktion und des inneren Stoffwechsels. *Acta med. Scandinav.*, 59:95-96, 1934.
611. FORSGREN, E. Über die Rhythmik der Leberfunktion, des Stoffwechsels und des Schlafes. Stockholm: Marcus, 1935. Pp. 56.
612. FÖRSTER, J. Über die normalen Werte des Bilirubin-Gehaltes im Blutserum. *Klin. Wchnschr.*, 4:Part II, 1689-90, 1925.
613. FORTUNATO, A. L'Acido urico enterotropico negli individui affetti da cirrosi epatica. *Folia med.*, 19:21-32, 1933.
614. FORTUNATO, A. Compartamento dell'acido urico della bile negli individui affetti da calculosi biliare. *Morgagni*, 76:1115-20, 1934.
615. FOSSEL, M. Gallen- und Gallenwegstudien. Über die Herkunft der Gallenamylasen. *Arch. f. d. ges. Physiol.*, 228:764-68, 1931.
616. FOSTER, M. G., and HOOPER, C. W. A quantitative method for analysis of bile acids in dog's bile. *J. Biol. Chem.*, 38:355-66, 1919.
617. FOSTER, M. G.; HOOPER, C. W.; and WHIPPLE, G. H. Normal fluctuations in healthy bile fistula dogs. *J. Biol. Chem.*, 38:367-77, 1919.
618. FOSTER, M. G.; HOOPER, C. W.; and WHIPPLE, G. H. The metabolism of bile acids. Administration by stomach of bile, bile acids, taurine, and cholic acid to show the influence upon bile acid elimination. *J. Biol. Chem.*, 38:379-92, 1919.
619. FOSTER, M. G.; HOOPER, C. W.; and WHIPPLE, G. H. The metabolism of bile acids; endogenous and exogenous factors. *J. Biol. Chem.*, 38:393-411, 1919.
620. FOSTER, M. G.; HOOPER, C. W.; and WHIPPLE, G. H. Metabolism of bile acids. Control of bile ingestion and food factors. *J. Biol. Chem.*, 38:413-20, 1919.
621. FOSTER, M. G.; HOOPER, C. W.; and WHIPPLE, G. H. Origin of taurocholic acid. *J. Biol. Chem.*, 38:421-33, 1919.
622. FOSTER, D. P., and WHIPPLE, G. H. Fibrin values influenced by cell injury, inflammation, intoxication, liver injury and the Eck fistula. *Am. J. Physiol.*, 58:407-31, 1921.
623. FOURCROY, A. F. *Système des connaissances chimiques*. Paris, 1801.
624. FOURCROY, A. F., and VAUQUELIN, L. N. Copie de quelques découvertes chimiques. *Ann. d. Chem.*, 6:177-82, 1790.
625. FOX, F. W. Composition of human bile. *Quart. J. Med.*, 21:107, 1927.
626. FRAENKEL, E., and KRAUSE, P. Bakteriologisches und Experimentelles über die Galle. *Ztschr. f. Hyg.*, 32:97-110, 1899.
627. FRANKE, K. Hautfarbe und Uringallenfarbstoffe beim Ikterus. *Ztschr. f. d. ges. exper. Med.*, 79:107-24, 1931.
628. FRANKE, K. Hautfarbe und Uringallenfarbstoffe beim Ikterus: Bilirubin und Biliverdin. *Ztschr. f. d. ges. exper. Med.*, 79:125-33, 1931.

629. FRÄNKEL, S. Gallenfarbstoffe. Descriptive Biochemie, pp. 448-62. Weisbaden: J. F. Bergmann, 1907.
630. FRASER, T. R. Note on the antivenomous and antitoxic qualities of the bile of serpents and of other animals. *Brit. M. J.*, 2:595, 1897; 2:627, 1898.
631. FREDERICQ, H. Action des entités chimiques présente; dans les sels biliaires sur le cœur isolé du lapin. *Arch. internat. de physiol.*, 15:220-27, 1919.
632. FRERICH, F. Th. Beiträge zur physiologischen und pathologischen Chemie der Galle, mit besonderer Berücksichtigung der Leberkrankheiten. *Ann. f. d. ges. Heilk.*, 5:30-48, 1845.
633. FRERICH, F. T. Injection von reiner Galle in das Blut lebender Thiere. *Klin. der Leberkrankheiten*, Braunschweig, 1:404-7, 1858.
634. *FRERICH, F. T. A clinical treatise on diseases of the liver. 2 vols. Breslau, 1858. CHARLES MURCHISON (tr.). London: New Sydenham Society, 1860.
635. FRERICH, F. T., and STADELER, G. Über die Umwandlung der Gallensäuren in Farbestoff. *Arch. f. Anat., Physiol. u. wissensch. Med.*, 1856, pp. 55-61.
636. FREUDE, E. Die Wirkung des 20% igen dehydrocholsäuren Natrium auf den Magen. *Therap. d. Gegenw.*, 68:388, 1927.
637. FREY, J. Kolloidosmotischer Druck der Galle und Chlorresorption der Gallenblase. *Ztschr. f. d. ges. exper. Med.*, 95:13-29, 1934.
638. FREY, S. Ein Versuch, die Gallensäuren im Serum ikterischer quantitativ zu erfassen. *Klin. Wchnschr.*, 42:1837, 1923.
639. FRIEDLÄNDER, V., and BARISCH, C. Zur Kenntnis der Gallenabsonderung. *Arch. f. Anat., Physiol. u. wissensch. Med.*, 1860, pp. 646-73.
640. FROMHOLDT and NERSESSOFF. Untersuchungen über den Pigmentstoffwechsel. *Biochem. Ztschr.*, 125:149-52, 153-57, 1921.
641. FROTHINGHAM, C., and MINOT, G. R. The effect of the injection of bovine bile into rabbits. *J. M. Research*, 27:79-82, 1912-13.
642. FRYER. Case of extravasation of bile into the cavity of the abdomen from rupture of the liver or gallbladder. *Tr. Med.-Chir. Soc., London*, 4:330-34, 1813.
643. FUBINI, S., and LUZZATI, M. Zur Physiologie des Darmes. Moleschotts Untersuchungen zur Naturlehre, 13:378-401, 1888.
644. FUCHS. Über Galleneinfloßungen ins Blutgefäß-System grösserer Haussäugethiere. *Amtl. Berl. u. d. Versamml. Deutsch. Naturf. u. Aerzte*, 1858, pp. 195-98. Carlsruhe, 1859.
645. FUENTES, B. V., and TERRA, J. V. y A. Acción de la mucosa de la vesicula biliar sobre la colessterins de la bilis. *Arch. argent. de enferm. d. apar. digest.*, 9:439-48, 1934.

646. FUJIMORI, H. Studies of icterus neonatorum. Jap. J. Obst. & Gynec., 16:258, 1933; 17:95, 235, 1934.
647. FUKASE, T. Glykogenie der Leber beim Hungern unter Einfluss von Insulin und Gallensäure. Arb. a. d. Med. Fak. Okayama, 4:537-42, 1935.
648. FUKASE, T. Bedeutung der Gallensäure im Kohlehydratstoffwechsel. Glykogenbildung der Leber unter Zufuhr von Hühnereibestandteilen mit Cholsäure. J. Biochem., 21:111-17, 1935.
649. FUKASE, T., and FUZIWARA, K. Über die Gallensäurebildung. Über den Einfluss der Nahrung auf den Gallensäuregehalt der Galle. J. Biochem., 15:193-96, 1932.
650. FUKUI, T. Bildung der 7-oxy-3,12-Diketocholansäure aus Dehydrocholsäure durch *Bacillus Coli Communis*. J. Biochem., 25:61-69, 1937.
651. FÜTTERER, G. Wie bald gelangen Bacterien, welche in die Portalvene eingedrungen sind, in den grossen Kreislauf und wann beginnt ihre Ausscheidung durch die Leber und die Nieren? Klin. Wchnschr., 36:58-59, 1899.
652. FUZITA, S. Die Bedeutung der Gallensäure im Kohlehydratstoffwechsel. Über den Einfluss der Gallensäure und der Phosphate auf die Zuckerassimilation. J. Biochem., 12:383-91, 1930; 13:219-36, 1931.
653. FUZIWARA, K. Phosphate im Harn bei Zufuhr von Gallensäure. J. Biochem., 13:43-56, 1931.
654. FUZIWARA, K. Über den Einfluss der Gallensäure auf den Calciumstoffwechsel. J. Biochem., 13:465-71, 1931.
655. FUZIWARA, K. Die Bedeutung der Gallensäure in Kohlenhydratstoffwechsel. Die Glykogenbildung der Leber bei splenektomierten Kaninchen unter dem Einfluss von Adrenalin, Cholsäure, und Milzextrakt. Biochem. Ztschr., 265:76-79, 1933.
656. GALENI, CLAUDII. Medicorum Graecorum opera omnia, 15:199. D. C. G. KÜHN (ed.). Lipsiae, 1821-33.
657. GALEOTTI-FLORI, A. Ricerche sperimentali su alcune proprietà biologiche dei taurocolato di sodio. Riv. di clin. pediat., 30:554-62, 1932.
658. GALIGANI, D. Action du glycocholate de soude et du desoxycholate de soude sur le développement en cultures du bacille tuberculeux. Boll. d. sez. ital., 6:303-7, 1934.
659. GAMBERINI, M. Idrope delle vie biliari (bile bianca). Arch. di pat. e clin. med., 10:549-79, 1931.
660. GAMBLE, J. L., and McIVER, M. A. Acid-base composition of pancreatic juice and bile. J. Exper. Med., 48:849-57, 1928.
661. GARDIEN, M. Ictère (des nouveau-nés). Dict. des sciences médicales, 23:463-73, 1818.

662. GARDNER, J. A., and GAINSBOROUGH, H. Blood cholesterol studies in biliary and hepatic disease. *Quart. J. Med.*, **23**:465-83, 1930.
663. GARGANO, C. Alterazioni del fegato consecutive ad iniezioni di bile. *Sperimentale*, *Arch. di biol.*, **90**:540-44, 1936.
664. GARNIER, M. Etudes de physiologie pathologique. Une lésion de l'ictère. *Presse méd.*, **40**:97-98, 1932.
665. GAUTIER, C., and DELEZENNE, C. Sur l'action anticoagulante du hépatopancréatique des crustacés. *Compt. rend. Soc. de biol.*, **78**:732-34, 1915.
666. GEILL, T. Studies on jaundice. *Hospitalstid.*, Copenhagen, **74**:211-27, 1094, 1931.
667. GEPTNER, F. K. [Chemical composition of bile in children.] Russian. St. Petersburg, 1900.
668. GÉRAUDEL, E. Ictère et sécrétion biliaire. *J. de physiol. et path. gén.*, **8**:103-14, 1906.
669. GERHARDT, C. Die Pathogenese des Ikterus. *Münch. med. Wchnschr.*, **52**:889, 1905.
670. GERHARDT, D. Über Leberveränderungen nach Gallengangsunterbindung. *Arch. f. exper. Path. u. Pharmacol.*, **30**:1-20, 1892.
671. GERLACH, W. Zur Gallenfarbstoffuntersuchung. *Therap. Monats.*, **17**:56, 1903.
672. GERONNE, A. Zur Pathogenese einiger Formen des Ikterus. *Klin. Wchnschr.*, **1**:828-32, 1922.
673. GERSTER, J. C. A. The feeding of bile collected from biliary fistulas in obstruction of the common duct. *J.A.M.A.*, **64**:1900, 1915.
674. GERTNER, W. K. Experimentelle Beiträge zur Physiologie und Pathologie der Gallensecretion. Jerjew (Dorpat): C. Mattiesen, 1893. Pp. 56.
675. GIBSON, R. H. On the origin of taurocholic acid. *J. Biol. Chem.*, **6**:16-17, 1909.
676. GIFFIN, H. Z., and SANFORD, A. H. Clinical observations concerning the fragility of erythrocytes. *J. Lab. & Clin. Med.*, **4**:465-78, 1919.
677. GILBERT, A., and CASTAIGNE, J. Note sur l'ictère acholurique. *Compt. rend. Soc. de biol.*, **51**:261-95, 1899.
678. GILBERT, A.; CHABROL, E.; and BÉNARD, H. La Cholémie saline dans les ictères. *Compt. rend. Soc. de biol.*, **83**:1602-5, 1920.
679. GILBERT, A., and HERSCHER, M. La Cholémie physiologique. *Presse méd.*, **14**:201-2, 1906.
680. GILBERT, A., and HERSCHER, M. Sur les variations de la cholémie physiologique. *Presse méd.*, **14**:209-11, 1906.
681. GILBERT, A., and HERSCHER, M. Sur la teneur en bilirubine du sérum sanguin dans l'obstruction chronique du canal cholédoque. *Compt. rend. Soc. de biol.*, **60-61**:208-11, 1906.

682. GILBERT, A., and HERSCHER, M. Sur la cholémie et la polycholie de l'ictère. *Compt. rend. Soc. de biol.*, 62:1010, 1907.
683. GILBERT, A., and HERSCHER, M. La Cholémie normale et pathologique. *Traité des maladies du sang.*, Paris: Baillière, 3:1913.
684. GILBERT, A.; LERÉBOULLET, P.; and STEIN, Mlle. Recherches comparatives sur la cholémie physiologique chez la mère et le nouveau-né. *Compt. rend. Soc. de biol.*, 55:847-59, 1903.
685. GILBERT, A., and LERÉBOULLET, P. Sur la teneur en bilirubine du sérum sanguin dans l'ictère simple du nouveau-né. *Compt. rend. Soc. de biol.*, 59:35-37, 1905.
686. GILBERT, A., and LERÉBOULLET, P. Xanthélasma et cholémie. *Compt. rend. Soc. de biol.*, 64:579-80, 1908.
687. GILBERT, E. Die Giftigkeit der Gallensäuren. *Ztschr. f. d. ges. exper. Med.*, 52:779-90, 1926.
688. GILMAN, A., and COWGILL, G. R. Osmotic relations between blood and body fluids. Pancreatic juice, bile and lymph. *Am. J. Physiol.*, 104:476-79, 1933.
689. GIORDANO, C., and LEVI, C. Studi sui sali biliari; metabolismo dei sali biliari negli itteri da assorbimento. *Arch. per le sc. med.*, 53:797-815, 1929.
690. GIORDANO, C.; MARENGO, G.; and GALIGANI, D. Metabolismo dei sali biliari negli itteri. *Arch. per le sc. med.*, 61:677-700, 1936.
691. GIRARDEAU, M. Le Foie et la bile dans le livre des mille et une nuits. Thèse de Paris, 1910, No. 107. Pp. 60.
692. GLAESSNER, K., and SINGER, G. Gallensäuren als Abführmittel. *Wien. klin. Wchnschr.*, 23:5-6, 1910.
693. GLASS, J. Über den Einfluss einiger Natriumsalze auf Secretion und Alkaliengehalt der Galle. *Arch. f. exper. Path. u. Pharmacol.*, 30:241-74, 1892.
694. GLEY, E., and LAMBLING, E. Sur les conditions dans lesquelles se manifestent les propriétés antiseptiques de la bile. *Rev. biol. de Nord de la France*, 1:7-12, 1888-89.
695. GLUR, W. Einwirkung von Galle auf das Froschherz. *Ztschr. f. Biol.*, 52:479-533, 1909.
696. GOLBER, L. M. Über den Gallenchemismus bei Schilddrüsenerkrankungen. Zur Frage der Ätiologie der Gallensteindiathese. *Arch. f. exper. Path. u. Pharmacol.*, 177:159-66, 1935.
697. GOLDBLOOM, A., and GOTTLIEB, R. Icterus neonatorum. *Am. J. Dis. Child.*, 38:57, 1929.
698. GORDON, A. S. Studies on the acceleration and inhibition of haemolysis. The effect of initial pH on saponin, taurocholate, and glycocholate haemolysis. *Quart. J. Exper. Physiol.*, 22:399-409, 1933.

699. GORODECKI, H. Über den Einfluss des experimentall in den Körper eingeführten Hämoglobins auf die Zusammensetzung der Galle. Diss., Dorpat, 1889.
700. GOSSET, A.; DESPLAS, B.; and BONNET, L. Les Perforations de la vésicule biliaire lithiasique. *J. de chir.*, **25**:257-82, 1925.
701. GOUPIL. Essai sur la physiologie du foie. Thèse de M. RENAUD. Strasbourg, 1838.
702. GOWDECKI. Über der Einfluss des experimentall in der Körper eingeführten Hemoglobins auf Secretion und Zusammensetzung der Galle. Inaug. Diss. Dorpat, 1889.
703. GRAEF, I., and STURTEVANT, M. Cholecystitis due to *Bacillus aerogenes-capsulatus*. *Arch. Surg.*, **28**:771-81, 1934.
704. GRAHAM, E. A.; COLE, W. H.; COPHER, S. H.; and MOORE, S. Diseases of the gallbladder and bile ducts, p. 385. Philadelphia: Lea & Febiger, 1928.
705. GRASSMANN, W., and BASU, K. P. Über die enzymatische Spaltbarkeit gepaarter Gallensäuren. *Ztschr. f. physiol. Chem.*, **198**:247, 1931.
706. GRAVES, A. M. Combined and separate effects of bile, pancreatic secretion and trauma in experimental peptic ulcer. *Arch. Surg.*, **30**:833-53, 1935.
707. GRAVES, R. J. Clinical lectures on the practice of medicine. J. M. NELIGAN (ed.). 2d ed. 2 vols. Dublin. 1848.
708. GRAWITZ, E. Klinisch experimentelle Blutuntersuchungen. *Ztschr. f. klin. Med.*, **22**:430-35, 1893.
709. GRAY, H. K., and McGOWAN, J. M. Liver damage in biliary disease: its relation to the concentration of bile acids in the bile. *Proc. Staff Meet. Mayo Clinic*, **12**:196-99, 1937.
710. GRAY, J. S., and IVY, A. C. Role of serum-calcium fractions in effect of viosterol on bleeding tendency in jaundice. *Am. J. Digest. Dis. & Nutrition*, **2**:368-72, 1935.
711. GREAVES, J. D., and SCHMIDT, C. L. A. Studies on calcium and phosphorus in bile-fistula dogs. *Proc. Soc. Exper. Biol. and Med.*, **29**:373-77, 1932.
712. GREAVES, J. D., and SCHMIDT, C. L. A. The role played by bile in the absorption of vitamin D in the rat. *J. Biol. Chem.*, **102**:101-12, 1933.
713. GREAVES, J. D., and SCHMIDT, C. L. A. On the absorption and utilization of carotene and vitamin A in choledochocolonostomized vitamin A deficient rats. *Am. J. Physiol.*, **111**:492-501, 1935.
714. GREENE, C. H., and ALDRICH, M. Studies in the metabolism of the bile acids. *Am. J. Physiol.*, **81**:480, 1927.

715. GREENE, C. H.; ALDRICH, M.; and ROWNTREE, L. G. Composition of the bile after intravenous injection of certain of its constituents. *J. Physiol.*, **64**:7-8, 1927.
716. GREENE, C. H.; ALDRICH, M.; and ROWNTREE, L. G. The entero-hepatic circulation of the bile acids. *J. Biol. Chem.*, **80**:753-60, 1928.
717. GREENE, C. H.; ALDRICH, M.; and SNELL, A. M. Studies in obstructive jaundice. *J. Clin. Investigation*, **2**:604, 1926.
718. GREENE, C. H.; HANDELSMAN, M. B.; and BABEY, A. M. Liver and biliary tract. *Arch. Int. Med.*, **59**:724-53, 1937.
719. GREENE, C. H.; McVICAR, C. S.; ROWNTREE, L. G.; and WALTERS, W. A comparative study of certain tests for hepatic function in patients with obstructive jaundice. *Arch. Int. Med.*, **36**:418, 1925.
720. GREENE, C. H., and SNELL, A. M. The sequence of changes in the blood and bile following the intravenous injection of bile or its constituents. *J. Biol. Chem.*, **78**:691-713, 1928.
721. GREENE, C. H.; SNELL, A. M.; and WALTERS, W. Functional tests in the surgical diagnosis and treatment of diseases of the liver and bile ducts. *J. Lab. & Clin. Med.*, **16**:765-74, 1931.
722. GREENE, C. H.; WALTERS, W.; and FREDRICKSON, C. H. The composition of the bile following the relief of biliary obstruction. *J. Clin. Investigation*, **9**:295-310, 1930.
723. GREGORY, R. A quantitative study of the Pettenkofer reaction for bile salts. *Proc. Soc. Exper. Biol. & Med.*, **24**:9:910, 1927.
724. GREULICHIO, J. G. *Χοληγογία* sive themata paradoxa de bile, pp. 1-129. Francofurti: Hermannum à Sande, 1682.
725. GRIFFITHS, W. J. Isolation from bile of pigment having direct van den Bergh reaction. *Biochem. J.*, **26**:1155-63, 1932.
726. GRIFFITHS, W. J., and KAYE, G. A study of the blood-pigment in obstructive jaundice, with observations on the van den Bergh reaction. *Brit. J. Exper. Path.*, **11**:441-46, 1930.
727. GRIGAUT, A. *Le Cycle de la cholestérine*. Thèse de doctorat. Paris, 1913.
728. GRIMBERT, L. *Procédés de recherche des éléments de la bile, de l'urobiline et de son chromogène dans les produits de l'organisme*. Paris méd., **14**:8, 1914.
729. GROB, F. *Über Bradykardie*. *Deutsches Arch. f. klin. Med.*, **42**:574-608, 1888.
730. GROLL, J. *De Invloed van gal en Galzouten op de Belangrijkste. Spijsverteringsfermenten*. *Neder. Tijdschr., v. Geneesk.*, **64**:1157-68, 1920.
731. GROLLEMUND, W. *Etude expérimental de l'action des acides biliaries sur l'organisme*. Thèse. Strassbourg, 1869. Pp. 74.

732. GROSS, R. E. Congenital anomalies of the gallbladder. *Arch. Surg.*, 32:131-62, 1936.
733. GSELL-BUSSE, M. A. Thelykinine in der Galle. *Klin. Wchnschr.*, 7-3:1606, 1928.
734. GSELL-BUSSE, M. A. Östrushormon in der Galle. *Arch. f. exper. Path. u. Pharmakol.*, 139:328-40, 1928.
735. GUCCI, G. Sul drenaggio delle vie biliari. *Policlinico (sez chir.)*, 40: 503-9, 1933.
736. GUINAUD, E. Sur les pancréatites chroniques avec ictère. Thèse No. 66. Paris, 1911. Pp. 62.
737. GUNDELACH, C., and STRECKER, A. Untersuchung des Schweinegalle. *Ann. d. Chem.*, 62:205-32, 1847.
738. GUNDERMANN, W. Zur Pathologie der Gallensekretion, zugleich ein Beitrag zur Polycholie. *Beitr. z. klin. Chir.*, 128:1, 1923.
739. GUNDERMANN, W. Experimentelle Gallenstudien. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, Jena, 39:353-76, 1926.
740. GUNTHER, L., and GREENBERG, D. M. The diffusible calcium and the proteins of the blood serum in jaundice. *Arch. Int. Med.*, 45: 983-1003, 1930.
741. GÜRBER, A., and HALLAUER, B. Über Eiweissausscheidung durch die Galle. *Ztschr. f. Biol.*, 45:372-79, 1904.
742. GUTZEIT, Prof. Dr., and KUHLEBAUM, Dr. Über die Darmmotilität beim Ikterus. *München. med. Wchnschr.*, 81:1095-98, 1934.
743. HABERLAND, H. F. O. Die Beziehungen des Ductus-Choledochus-Verschlusses zum Ikterus. *Arch. f. klin. Chir.*, 135:248-80, 1925.
744. HAESSLER, H., and STEBBINS, M. G. Effect of bile on the clotting time of blood. *J. Exper. Med.*, 29:445-49, 1919.
745. HALBERSTAM, M. Beitrag zur Lehre vom Icterus Neonatorum. Diss. Dorpat, 1885. Pp. 35.
746. HALL, W. W. Van den Bergh reaction for serum bilirubin. *J. Lab. & Clin. Med.*, 12:529, 1927.
- 747.*HALLER, ALBERTO V. *Elementa physiologiae corporis humani. Bilis.* Bernae, 6:542-615, 1764.
748. HALLION, L., and NEPPER, H. Influence excito-motrice de la bile sur l'intestin. *Compt. rend. Soc. de biol.*, 63:182-84, 254-57, 1907.
749. HALSTED, W. S. Retro-injection of bile into the pancreas, a cause of acute hemorrhagic pancreatitis. *Bull. Johns Hopkins Hosp.*, 12:179-82, 1901.
750. HAMMARSTEN, O. Über Dehydrocholsäure, ein neues Oxydationsprodukt der Cholsäure. *Biochem. Ztschr.*, 14:71, 1881.
751. HAMMARSTEN, O. Zur Kenntnis der Lebergalle der Menschen. *Ges. d. Wiss., Upsala*, 15:6, 1893.

752. HAMMARSTEN, O. Untersuchungen über die Gallen einiger Polarthiere. *Ztschr. f. physiol. Chem.*, **36**:524-55, 1902.
753. HAMMARSTEN, O. Zur Chemie der Galle. *Ergebn. d. Physiol.*, **4**:1-22, 1904.
754. HAMMARSTEN, O. Über die Darstellung kristallisierter Taurocholsäure. *Ztschr. f. physiol. Chem.*, **43**:127-44, 1904.
755. HAMMARSTEN, O. Textbook of physiological chemistry. JOHN A. MANDEL (tr). 5th ed. The Scientific Press, Robert Drummond & Co., New York: 1908.
756. HAMMARSTEN, O. Über die Gallen einiger Seehunde. *Ztschr. f. physiol. Chem.*, *Strassb.* **68**:109-18, 1910.
757. HAMMARSTEN, O. Untersuchungen über die Galle des Nilpferdes. *Ztschr. f. physiol. Chem.*, **74**:123-41, 1911.
758. HANOT, V. C. La Cirrhose hypertrophique avec ictère chronique. Paris: Rueff, 1892. Pp. 182.
759. HANOT, V. La Bile incolore; acholie pigmentaire. *Semaine méd.*, **23**:197, 1895.
760. HANSON, S. Undersogelser over Galdens Bacteriologi. *Hospitalstid.*, **69**:289-99, 1926.
761. HANSEN, E., and YUREVICH, A. Bacteriological observations in disease of the biliary tract. *Am. J. Digest. Dis. & Nutrition*, **2**:460-66, 1935.
762. HARKINS, H. N., and HARMON, P. H. Surgical shock as a lethal factor in bile peritonitis. *Proc. Inst. Med. Chicago*, **11**:56-57, 1936.
763. HARKINS, H. N.; HARMON, P. H.; HUDSON, J.; and ANDREWS, E. Mechanism of death in bile peritonitis. *Proc. Soc. Exper. Biol. & Med.*, **32**:691-93, 1935.
764. HARKINS, H. N.; HARMON, P. H.; and HUDSON, J. Lethal factors in bile peritonitis. *Arch. Surg.*, **33**:576-608, 1936.
765. HARKINS, H. N.; HARMON, P. H.; and HUDSON, J. E. Peritonitis due to bile and liver autolysis. *J.A.M.A.*, **107**:948-53, 1936.
766. HARLEY, G. Jaundice, its pathology and treatment. London: WALTON & MABERLY, pp. xviii+136. 1863.
767. HARLEY, V. The pathology of obstructive jaundice. *Brit. M. J.*, **2**:397-400, 1892.
768. HARLEY, V. Interference with icterus in occluded ductus choledochus. *Proc. Roy. Soc. Med.*, **51**:113-16, 1892.
769. HARLEY, V., and BARRETT, W. An experimental enquiry into the formation of gall-stones. *J. Physiol.*, **29**:341-51, 1903.
770. HARMON, P. H., and HARKINS, H. N. Peritonitis. *Arch. Surg.*, **34**:565-79, 580-90, 1937.
771. HARPUDER, K. Galle- und Purin-stoffwechsel. *Klin. Wchnschr.*, **2**:436-38, 1923.

772. HARRIS, K. E. Acholuric jaundice associated with purpura. *Proc. Roy. Soc. Med.*, **26**:369, 1933.
773. HARROP, G. A., JR., and BARRON, E. S. G. The excretion of intravenously injected bilirubin as a test of liver function. *J. Clin. Investigation*, **9**:577-87, 1931.
774. HARTMAN, H. R. A study of the cause of jaundice in four hundred cases. *Med. Clin. N. Am.*, **2**:1383-88, 1928.
775. HARTOCH, W. Zur Morphologie der Leber- und Nierensekretion: Lebendbeobachtungen im Lumineszenzlicht. *Ztschr. f. d. ges. exper. Med.*, **79**:538, 1931.
776. HASEGAWA, T. Einfluss der Gallensäure auf die Ausscheidung des Kochsalzes, Kaliums und Natriums im Harn. *J. Biochem.* **19**:403-7, 1934.
777. HASEGAWA, T. Einfluss der Gallensäure auf die Zuckerassimilation des Hundes mit Pankreasdiabetes. *Arb. a. d. med. Fak. Okayama*, **4**:453-60, 1935.
778. HASHIGUCHI, F. Über die haemolytische Wirkung der Gallensäure. *J. Kumamoto M. Soc.*, **10**:647, 1934.
779. HATAKEYAMA, T. Über den Eiweissstoffwechsel und Phosphorsäurebestand bei dem experimentellen, haemolytischen und Stauungsikterus. *J. Biochem.*, **8**:261-73, 1928.
780. HATAKEYAMA, T. Bedeutung der Gallensäure im Kohlehydratstoffwechsel. *J. Biochem.*, **11**:273-83, 1929.
781. HATAKEYAMA, T., and OKAMURA, T. Über die Kenntnis von der Fischgalle. *J. Biochem.*, **9**:333-35, 1928.
782. HATERIUS, H. O.; PFIFFNER, J. J.; and NELSON, W. O. The possible oestrus-inducing effect of commercial taurocholate. *Proc. Soc. Exper. Biol. & Med.*, **26**:820-22, 1929.
783. HAWKINS, W. B., and BRINKHOUS, K. M. Prothrombin deficiency the cause of bleeding in bile fistula dogs. *J. Exper. Med.*, **63**:795-801, 1936.
784. HAWKINS, W. B.; SRIBHISHAJ, K.; ROBSCHKEIT-ROBBINS, F. S.; and WHIPPLE, G. H. Bile pigment and hemoglobin interrelation in anemic dogs. *Am. J. Physiol.*, **96**:463-76, 1931.
785. HAWKINS, W. B., and WHIPPLE, G. H. Bile fistulas and related abnormalities: osteoporosis, cholelithiasis and duodenal ulcers. *J. Exper. Med.*, **62**:599-620, 1935.
786. HAYAKAWA, H. Über die Entgiftung durch die Galle. *Keijo Igakku*, Nos. 7, 11, 87. 1945-72, 1927-28.
787. HAYASHI-INOBUKE and ARAKAWA-SHINYA. Über die Durchlässigkeit des Magendarmkanals für artfremde Eiweisskörper bei Leberfunktionsstörung. *Nagoya J. M. Sc.*, **7**:1-25, 1933.

788. HEINLEIN, H. Die quantitative Zusammensetzung der Galle unter normalen und pathologischen Verhältnissen mit besonderer Berücksichtigung von Lebererkrankungen. *Krankheitsforschung*, 9: 185-210, 1931.
789. HEINTZ, W., and WISLICENUS, J. Über die Gänsegalle und die Zusammensetzung der Taurochenocholsäure. *Poggendorffs Ann. Physik u. Chem.*, 108:547-67, 1859.
790. HELLER, J. F. Pathologische Chemie des Icterus und des Gallenfarbstoffes in den verschiedenen Se- und Exkreten. *Wien. med. Wchnschr.*, 1:193, 209, 225, 1851.
791. HELLMUTH, K. Untersuchungen über Bilirubinämie beim Neugeborenen, zugleich ein Beitrag zur Genese des Icterus neonatorum. *Monatschr. f. Geburtsh. u. Gynäk.*, 54:341-51, 1921.
792. HELLSTRÖM, J. Choleic acid enteroliths. *Acta chir. Scandinav.*, 64: 79, 1928.
793. HELLSTRÖM, J. Ytterligare ett fall av choleinsyreenterolit. *Hygiea*, 98:480-83, 1936.
794. HELWIG, F. C., and ORR, T. G. Traumatic necrosis of the liver with extensive retention of creatinine and high grade nephrosis. *Arch. Surg.*, 24:135-44, 1932.
795. HELWIG, F. C., and SCHUTZ, C. B. A liver kidney syndrome. *Surg. Gynec. Obst.*, 55:570-80, 1932.
796. HENCH, P. S. Analgesia accompanying hepatitis and jaundice in cases of chronic arthritis, fibrositis and sciatic pain. *Proc. Staff Meet. Mayo Clinic*, 8:430-36, 1933.
797. HENCH, P. S. A clinic on some diseases of joints: the inactivating effect of jaundice. *M. Clin. N. Am.*, 19:551-83, 1935.
798. HENLE, J. Braunschweig. *Handbuch der rationellen Pathologie*, 2: 205, 1847.
799. HENRICHSBORFF. Über die Natur der Gallenkörperchen. *Virchows Arch. f. path. Anat.*, 239:64, 1922.
800. HERBERT, F. K. Plasma phosphatase in various types of jaundice. *Brit. J. Exper. Path.*, 16:365, 1935.
801. HERMANN, E., and KORNFELD, F. Physiologische Graviditätsbilirubinämie. *Wien. klin. Wchnschr.*, 37:1215, 1924.
802. HERMANN, E., and KORNFELD, F. Zur Frage der Bilirubinaemie in Schwangerschaft. *Zentralbl. f. Gynäk.*, 49:2227-29, 1925.
803. HERMANN, Max. De effectu sanguinis diluti in secretionem urinae. *Diss. Inaug. Berolini*, 1859.
804. HERRING, P. T., and SIMPSON, S. The pressure of bile secretion and the mechanism of bile absorption in obstruction of the bile duct. *Proc. Roy. Soc. Med.*, 79:517-32, 1907.

805. HERZFELD, E., and HAEMMERLI, A. Die Galle im Stoffwechsel. *Schweiz. med. Wchnschr.*, 5:141-45, 1924.
806. HESS, A. F. A study of icterus neonatorum by means of the duodenal catheter. *J. Exper. Med.*, 11:673, 1909.
807. HESS, A. F. A study of icterus neonatorum by means of the duodenal catheter. *Am. J. Dis. Child.*, 3:304, 1912.
808. HESS, A. F. A consideration of the pancreas and its ducts in congenital obliteration of the bile ducts. *Arch. Int. Med.*, 10:37, 1912.
809. HESS, A. F. The secretion of bile in icterus neonatorum. *Am. J. Dis. Child.*, 11:405, 1916.
810. HETÉNYI, G. Die Funktionsprüfung der Leber mittels gleichzeitiger Bilirubinbestimmung im Blutserum und in der Galle. *Ztschr. f. klin. Med.*, 95:469-90, 1922.
811. HEWLETT, A. W. The effect of the bile upon the ester splitting action of pancreatic juice. *Bull. Johns Hopkins Hosp.*, 16:20, 1905.
812. HEYD, C. G.; KILLIAN, J. A.; and KLEMPERER, P. Pathogenesis of jaundice. *Surg. Gynec. Obst.*, 44:489-500, 1927.
813. HEYMANN, W. Untersuchungen über die phosphatstoffwechselstörung bei Rachitis. Über Rachitis und Tetanie bei Gallen fistelhunden. *Ztschr. f. Kinderh.*, 54:201-22, 1933.
814. HEYMANN, W. Nitrogen, potassium, sodium and chlorine metabolism in rickets, with special reference to biliary fistula rickets in puppies. *J. Exper. Med.*, 64:471-83, 1936.
815. HIKOSAKA, R., and NAKASHIMA, K. Ikterus Dissociaticus. Eine neue klinische Klassifikation der Leberkrankheiten. *Jap. J. Gastroenterol.*, 6:408-13, 1934.
816. *HILDENBRAND, T. Über die Wirkung der Cholsäure auf das Froschherz. *Diss. Inaug.*, Würzburg, 1920.
817. HILGERMANN, R. Die Chemotherapie der Pneumokokkeninfektion. *München. med. Wchnschr.* 77:1480-83, 1930.
818. HILGERMANN, R. Chemotherapie mit gallensäuren Alkalien, ein sicheres Heilmittel bei Streptokokkeninfektionen. *Deutsche med. Wchnschr.*, 62:883-84, 1936.
819. HILLYARD, L. V. Effect of denervation of liver on secretion of bile. *Am. J. Physiol.*, 97:612-14, 1931.
820. HINGLAIS, H. L'Origine chimique de la bilirubine et le rôle de la cellule hépatique dans sa formation. *Presse méd.*, 34:1030-33, 1926.
821. HINGLAIS, H. Les Théories récentes sur l'origine extra-hépatique de la bilirubine et leur application à la physiologie normale. *Presse méd.*, 34:1078-80, 1926.
822. HIPPOCRATES. *Medicorum graecorum opera—quae exstant*. D. C. G. KÜHN (ed.). Lipsiae, 1825-27.

823. HIPPOCRATES. *Cœuvres complètes*. E. LITTRÉ (ed.). Paris, 1839-61.
824. HIROKAWA, W. Über den Keimgehalt der menschlichen Galle und ihre Wirkung auf Bakterien. *Centralbl. f. Bakteriologie*, 53:12-36, 1909.
825. HIYEDA, K. Experimentelle Studien über den Ikterus. Ein Beitrag zur Pathogenese des Stauungsikterus. *Beitr. z. Path. Anat. u. z. allg. Pathol.*, 73:541-65, 1924-25.
826. HOESCH, K. Über neuere Gallenblasendiagnostik. *München. med. Wchnschr.*, 9:369, 1926.
827. HOFBAUER, J. Effect of bile salts on the automatic contractions of uterus. *Am. J. Obst. Gynec.*, 16:245-54, 1928.
828. HOFFMANN, H. Zur Verdauungslehre. *Hülers Arch.*, 6:157-88, 1844.
829. HOFMANN, F. *Bilis medicina et venenum corporis. Opera omnia phys. med.*, 6:151, 1748.
830. HOHLWEG, H. Über Störungen der Salzsäureabscheidung des Magens bei Erkrankungen und nach Extirpation der Gallenblase. *Deutsches Arch. f. klin. Med.*, 108:255-6, 1912.
831. HOKAN, R. Der Einfluss von Decholin auf den vespatorischen Umsatz von Ratten. *Biochem. Ztschr.*, 200:401, 1928.
832. HOLMES, J. B. Congenital obliteration of the bile ducts. *Am. J. Dis. Child.*, 11:405-31, 1916.
833. HONGO, S. Biochemical studies on lipins: on the amounts of lecithin, total cholesterol, free cholesterol, and cholesterol ester in the organ tissues of guinea pigs fed on a vitamin C free diet, and the ratios among these lipins. *Sei-I-Kwai M. J.*, 53:1-2, 1934.
834. HÖNNER, J. Über die Anwesenheit der Gallensäuren im normalen Harn. *Inaug. Diss. Dorpat*, 1873.
835. HOOPER, C. W. The influence of bile constituents on bile pigment secretion, taurocholic, glycocholic and cholic acids and bile fat. *Am. J. Physiol.*, 42:280-89, 1917.
836. HOOPER, C. W., and WHIPPLE, G. H. Bile pigment metabolism. *Am. J. Physiol.*, 40:332-59, 1916.
837. HOOPER, C. W., and WHIPPLE, G. H. Influence of fresh bile feeding upon whole bile and bile pigment secretion. *Am. J. Physiol.*, 42:264-79, 1917.
838. HOOPER, C. W., and WHIPPLE, G. H. Bile pigment output influenced by hemoglobin injection; splenectomy and anemia. *Am. J. Physiol.*, 43:275-89, 1917.
839. HOOVER, C. F., and BLANKENHORN, M. A. Dissociated jaundice. *Arch. Int. Med.*, 18:289, 1916.
840. HOPPE, F. Nachweis der Gallensäuren im Harn bei Ikterus. *Virchows Arch. f. path. Anat.*, 13:101-2, 1858.

841. HOPPE, F. Freie Cholsäure in den Excrementen von Hunden; Einwirkung der Cholsäure auf die Blutzellen im lebenden Thiere. *Virchows Arch. f. path. Anat.*, 25:181-83, 1862.
842. HOPPE-SEYLER, F. Über die Anwesenheit von Gallensäuren im icterischen Harn und die Bildung des Gallenfarbstoffes. *Virchows Arch. f. path. Anat.*, 24:1-13, 1862.
843. HOPPE-SEYLER, F. Über die Schicksale der Galle im Darmkanale. *Virchows Arch. f. path. Anat.*, 26:519-37, 1863. *Centr. med. Wissensch.*, 1:325-28, 1863.
844. HOPPE-SEYLER, F. *Handbuch der physiologisch und pathologisch chemischen Analyse*. Berlin: Hirschwald, 1865. Pp. 404.
845. HOPPE-SEYLER, F. *Untersuchung der Galle. Handbuch der physiologisch und pathologisch chemischen Analyse*. Berlin: Hirschwald., 8:706-17, 1909.
846. HORACZEK, P. J. *Die gallige Dyscrasie (Icterus)*. Wien, 1843. Pp. 143.
847. HORIYE, Y. *Untersuchen über die Beziehungen zwischen Cholesterinstoffwechsel und Bildung der Gallensäure*. *Biochem. Ztschr.*, 202: 409-20, 1928.
848. HORRALL, O. H. *Bile peritonitis*. Thesis. University of Chicago, 1925.
849. HORRALL, O. H. *Toxicity of bile*. Thesis. University of Chicago, 1927.
850. HORRALL, O. H. *The toxic substances in bile*. *Proc. Inst. Med. Chicago*, 6:254-56, 1927.
851. HORRALL, O. H. *The toxicity of bile*. *University of Chicago Science Series*, 6:287, 1927-28.
852. HORRALL, O. H. *Bilirubin, a non-toxic substance*. *J. Lab. & Clin. Med.*, 14:217-24, 1928.
853. HORRALL, O. H. *Toxicity of bile*. *Proc. Inst. Med. Chicago*, 7:178-79, 1928-29.
854. HORRALL, O. H. *Experimental bile peritonitis and its treatment in the dog*. *Arch. Int. Med.*, 43:114-28, 1929.
855. HORRALL, O. H. *In Symposium on jaundice: discussion*. *J.A.M.A.*, 95:1073, 1930.
856. HORRALL, O. H., and CARLSON, A. J. *The toxic factor in bile*. *Am. J. Physiol.*, 85:591-606, 1928.
857. HORSTERS, H. *Grundlagen und Erfolge der Anwendung gallensäurer Verbindungen bei Leber- und Gallenblasenerkrankungen*. *Fortschr. d. Therap.*, 6:467, 1930.
- 858.*HORSTERS, H. *Physiologie und Pathologie der Galle*. *Ergebn. d. Physiol.*, 34:494-582, 1932.

859. HOSHIZIMA, T. Einfluss der Gallensäure auf den Calciumstoffwechsel. Thyreoparathyreoprive Tetanie und Kalkzustand im Blut der Hündin bei Zufuhr von Gallensäure. *J. Biochem.*, 22:375-83, 1935.
860. HOSHIZIMA, T. Über Tauroisolithocholsäure aus Hühnergalle. *J. Biochem.*, 12:393-97, 1930.
861. HOSHIZIMA, T. Einfluss der Gallensäure auf den Calcium- Stoffwechsel. Veränderungen im Kalkzustand durch Zufuhr von Gallensäure bei normaler sowie thyreopara-thyreopriver Hündin. *J. Biochem.*, 17:29-45, 1933.
862. HOSONO, S. [Influence of bile acids upon gastric secretions.] Japanese. *Jap. J. Gastroenterol.*, 6:577, 1931.
863. HOWARD, C. P., and WOLBACH, S. B. Congenital obliteration of the bile ducts. *Arch. Int. Med.*, 8:1911, 557.
864. HOWELL, W. H., and HOLT, E. Two new factors in blood coagulation-heparin and pro-antithrombin. *Am. J. Physiol.*, 47:328-41, 1918.
865. HUBBARD, R. S., and ALLISON, C. B. Comparison of icteric index and direct v. d. Bergh test. *Proc. Soc. Exper. Biol. & Med.*, 26:438-39, 1929.
866. HUGHES, T. A., and SAHAI PREM NATH. Effect of bile salt (sodium taurocholate) on gastric secretion. *Indian Jour. Med. Res., Calcutta*, 17:No. 2, 453-60, 1929.
867. HUMMEL, R. Über die Beziehungen der Gallensäuren zum Nahrungscholesterin. *Ztschr. f. physiol. Chem.*, 185:105-15, 1929.
868. HUNEFELD, F. L. *Der Chemismus der tierischen Organisation*. Leipzig, 1840. Pp. 269.
869. HUNT, T. C. Bilious migraine: its treatment with bile salt preparations. *Lancet*, 225:279-85, 1933.
870. HUNTER, G. On the two types of bilirubin in serum. *Brit. J. Exper. Path.*, 11:415-19, 1930.
871. HUNTER, W. Toxaemic jaundice. *Brit. Med. J.*, 2:400-402, 1892.
872. HUNTER, W. Jaundice. In C. ALLBUTT and H. D. ROLLESTON, *A system of medicine*, 4:66-98, 1908.
873. HUPPERT, H. Über das Schicksal der Gallensäuren im Icterus. *Arch. d. Heilk.*, 5:236-56, 1864.
874. HUPPERT, H. Zur Gallenfarbstoffprobe. *Arch. d. Heilk.*, 8:476-77, 351-56, 1867.
875. HYNEMANN, T. Ikterus und Schwangerschaft. *Zentralbl. f. Gynäk.*, 50:2181-85, 1926.
876. IKOMA, S. Über den Einfluss einiger Gallensäuren auf den Fettstoffwechsel. *J. Biochem.*, 6:383-93, 1926.
877. IKOMA, S. Über die Kenntnis von der Fischgalle. Die Galle von *Serola quinquerediata*. *J. Biochem.*, 7:205-8, 1927.

878. ILLINGWORTH, C. F. W. The gallbladder in animals. *Edinburgh M. J.*, 43:458-61, 1936.
879. ILLIPO, A. Ikterus neonatorum und Gallenfarbstoffsekretion beim Foetus und Neugeborenen. *Ztschr. f. Kinderh.*, 9:208, 1913.
880. INABA, M. Über die Wirkung der Gallensäuren auf die Blutgerinnung. *Jap. J. M. Soc. Tr.*, Sec. IV, *Pharmacol.*, 8:122, 1934.
881. INABA, M. Über die Wirkung der Gallensäuren auf die Blutgerinnung. *Okayama-Igakkai-Zasshi*, 47:547-48, 1935.
882. INOUE, H. Studien über Indikan. Über Indikanausscheidung in der Galle. *J. Chosen M. A. (abst. sect.)*, 25:144, 1935.
883. ISAAC, S. Die klinischen Funktionsstörungen der Leber und ihre Diagnose. *Ergebn. d. inn. Med. u. Kinderh.*, 27:423-506, 1925.
884. ISHIDA, I. Über den Calcium- und Phosphorstoffwechsel. Einfluss des Carotins und Gallosterins auf den Kalk sowie Phosphorgehalt des Blutes. *J. Biochem.*, 20:5-16, 1934.
885. ISHII, K. A preliminary report on the antagonistic action of cholesteryl oleate to bile salts in gastric ulcer formation. *Med. Bull. Univ. Cincinnati*, 6:130-33, 1931.
886. ISHII, K. Studies on bile salts: preliminary report on antagonistic action of cholesteryl oleate to bile salts in gastric ulcer formation. *Sei-I-Kwai M. J. (abst. sect.)*, 53:5-6, 1934.
887. ISHII, K. Contribution to studies on antagonistic action of lipids to toxic action of bile salts. *Sei-I-Kwai M. J.*, 53:6-8, 1934.
888. ISHII, K. Contribution to studies on relationship between toxicity of bile salt and its antagonist. *Sei-I-Kwai M. J. (abst. sect.)*, 53:9-10, 1934.
889. ISHIYAMA, F. Ein Fall von sog. intermittierender weisser Galle und ihr Entstehungsmechanismus. *Jittika to Rinsho*, 10:1, 1933.
890. ISIBASI, M.; OKADA, T.; and UZI, T. Stammt das Blutbilirubin bei Choledochusunterbindung von der Galle ab? *Tr. Soc. path. jap.*, 24:181-83, 1934.
891. IRÔ, R. Über den Einfluss der kurzwelligen Strahlen auf Pharmaka; über den Einfluss der ultravioletten Strahlen auf die Entgiftungswirkung des glykocholsauren Natriums. *Folio pharmacol. japon. (Brev.)*, 12:9-10, 1931.
892. IROI, M. The effect of the presence of various salts on the surface tension of sodium taurocholate solution. *J. Biochem.*, 12:83-105, 1930.
893. ITOO, T. Das Puffervermögen und die Reaktion der Galle und das vegetative Nervensystem. *Biochem. Ztschr.*, 254:50-58, 1932.
894. IYI, A. C. Physiologic disturbances incident to obstructive jaundice. *J.A.M.A.*, 95:1068-72, 1930.

895. IVY, A. C. Symposium on gallbladder disease. Bull. Chicago Med. Soc., 33:22-30, 1931.
896. IVY, A. C. The physiology of the gall bladder. Physiol. Rev., 14:1-102, 1934.
897. IVY, A. C., and BERGH, G. S. The applied physiology of the extra-hepatic biliary tract. J.A.M.A., 103:1500-1504, 1934.
898. IVY, A. C.; SHAPIRO, P. F.; and MELNICK, P. The bleeding tendency in jaundice. Surg. Gynec. Obst., 60:781-84, 1935.
899. IVY, A. C., and WALSH, E. L. Observations on the etiology of gallstones. Ann. Int. Med., 4:134-44, 1930.
900. IWADO, M. Über den Einfluss der Gallensäure auf den Kalziumstoffwechsel. Kalkausscheidung in Harn unter dem Einfluss von Gallensäure und Milzextrakt. Arb. a. d. Med. Fak. Okayama., 4:346-55, 1935.
901. IWADO, M. Über den Einfluss der Gallensäure auf den Kalziumstoffwechsel. Blutkalkgehalt von normalen sowie von splenektomierten Kaninchen unter dem Einfluss von Gallensäure und Milz. Arb. a. d. med. Fakultät Okayama, 4:356-64, 1935.
902. IWADO, M. Blutkalkgehalt des normalen und splenektomierten Kaninchens unter dem Einfluss des Extraktes der normalen sowie der splenektomierten Leber mit Milzextrakt und Gallensäure. Arb. a. d. med. Fakultät Okayama, 4:424-37, 1935.
903. IWATO, M., and WATANABE, K. Vorkommen des Taurocholates in der Schlangen- und Katzensgalle. J. Biochem., 21:211, 1935.
904. JACCOUD, S. Traité de pathologie interne. 4th ed. Paris: Delahayi, 1877.
905. JACOBSEN, O. Untersuchung menschlicher Galle. Ber. d. deutsch. chem. Gesellsch., 6:1026-28, 1873.
906. JAFFE, M. De bilis pigmentorum genesi. Berolini, 1862.
907. JAFFE, M. Zur Lehre von den Eigenschaften und der Abstammung der Harnpigmente. Virchows Arch. f. path. Anat., 47:405-27, 1869. Centralbl. f. d. med. Wissensch., 1868, p. 233; 1871, p. 465.
908. JAGIC, N. Normale und pathologische Histologie der Gallencappilaren. Ein Beitrag zur Lehre vom Ikterus und der biliären Cirrhose. Beitr. z. path. Anat. u. z. allg. Path., 33:302-26, 1903.
909. JANKAU, L. Über Cholesterin und Kalkausscheidung mit der Galle. Arch. f. exper. Path. u. Pharmakol., 29:237, 1891.
910. JANKUBOVITCH, V. F. [Quantity and composition of bile in new-born and nursing infants.] Russian. Russk. Med., St. Petersburg., 3:754, 1885.
911. JARDON, L. Contribution à l'étude du pouvoir antitoxique de la bile. Lyon, 1896.

912. JASTROW, M. The liver in antiquity and the beginnings of anatomy. Univ. Penn. M. Bull., 20:238-54, 1908.
913. JAVILLIER, M. De l'hématine à la bilirubine et à l'urobiline. Soc. de chim. biol., 8:664-703, 1926.
914. JEGOROFF, K. Über Nachweis von Bilirubin in der Haut ikterischer. Deutsche med. Wchnschr., 57:539-40, 1931.
915. JENEY, E. Über die unmittelbare Wirkung der Gallenbestandteile auf das Knochenmark. Virchows Arch. f. path. Anat., 280:306-10, 1931.
916. JENKE, M. Bemerkungen zu der Arbeit. Zur polarimetrischen Gallensäurebestimmung in Körperflüssigkeiten und Organen. Arch. f. exper. Path. u. Pharmakol., 159:180-82, 1931.
917. JENKE, M. Über den Stoffwechsel der Gallensäuren. Arch. f. exper. Path. u. Pharmakol., 163:175-218, 1931.
918. JENKE, M., and STEINBERG, F. Über den Nachweiss der Gallensäuren im Blut. Arch. f. exper. Path. u. Pharmakol., 153:244-56, 1930.
919. JOHANNESSEN, C. Akut cholecystit uten sten, med spontau perforation av geldeblaeren. Norsk. mag. f. laegevidensk., 88:593-97, 1927.
920. JOHANNSON, S. De la périhépatite bilieuse avec épanchement biliaire dans le péritoine sans perforation de l'appareil biliaire. Rev. de chir., 46:892-902, 1912.
921. JOHNSON, L. W., and DICKENS, P. F. Differential diagnosis of surgical from nonsurgical jaundice by laboratory methods. Am. J. M. Sc., 176:690-707, 1928.
922. JOHNSON, W. R.; SHIONOYA, T.; and ROWNTREE, L. Extracorporeal thrombosis in experimental obstructive jaundice and after the intravenous administration of bile acids. J. Exper. Med., 48:871, 1928.
923. JOHNSTON, C.; RAVDIN, I.; AUSTIN, J.; and MORRISON, J. The absorption of calcium from the bile-free gall bladder. Am. J. Physiol., 99:648-55, 1932.
924. JOLLES, A. Beiträge zur Kenntnis der Gallenfarbstoffe. Arch. f. d. ges. Physiol., 75:446, 1899.
925. JOLLES, A. Über den Nachweis von Gallensäuren. Ber. d. deutsch. chem. Gesellsch., 41:2766, 1908.
926. JOLTRAIN, E., and WALTON, A. C. R. Etude sur le rôle joué par les sels biliaires sur la vitesse de sédimentation des hématies. Rev. de méd., 47:143-63, 1930.
927. JONES, K. K. A comparison of the buffer value of bile and pancreatic juice secreted simultaneously. Proc. Soc. Exper. Biol. & Med., 28:567-68, 1931.

928. JONES, K. K., and LAING, G. H. The effect of viosterol on the calcium content of dog's bile. *Am. J. Physiol.*, **110**:471-76, 1934.
929. JONES, K. K., and SHERBERG, R. O. Observations on the analysis of the saponifiable and non-saponifiable matter in bile. *Am. J. Physiol.*, **116**:87-88, 1936.
930. JONES, K. K., and SHERBERG, R. O. Are neutral fat and lecithin present in gall bladder bile? *Proc. Soc. Exper. Biol. & Med.*, **35**: 535-37, 1937.
931. JONES, T. B., and SMITH, H. P. The blood fibrinogen level in hepatectomized dogs and an outline of a method for the quantitative determination of fibrinogen. *Am. J. Physiol.*, **94**:144-61, 1930.
932. JORDAN, E. O. The inhibitive action of bile upon *B. coli*. *Tr. Chicago Path. Soc.*, **9**:44, 1913.
933. JORDAN, F. M., and GREENE, C. H. Anemia in jaundice. The formation of hemoglobin in experimental obstructive jaundice. *Am. J. Physiol.*, **91**:409-22, 1930.
934. JORDAN, F. M., and McVICAR, C. S. Anemia in jaundice. *Am. J. M. Sc.*, **179**:654-59, 1930.
935. JOSEPHSON, B. Die Dissoziationskonstanten der Gallensäuren. *Biochem. Ztschr.*, **263**:428-43, 1933.
936. JOSEPHSON, B. The optical properties of some bile acids. *Biochem. J.*, **29**:1484-89, 1935.
937. JOSEPHSON, B., and LARSSON, H. Über die Periodizität der Gallensekretion bei einem Patienten mit Gallenfistel. *Skandin. Arch. f. Physiol.*, **69**:227-36, 1934.
938. JOSEPHSON, B., and RYDIN, A. The resorption of the bile acids from the intestines. *Biochem. J.*, **30**:2224-28, 1936.
939. JOSLIN, E. P. Influence of bile on metabolism. *J. Bost. Soc. M. Sc.*, **3**:259-63, 1898-9.
940. JOST AUS KLOSTERS, E. Über die antiparasitäre Wirkung der Galle. Würzburg, 1887. Pp. 22.
941. JUDD, E. S. Relation of the liver and the pancreas to infection of the gallbladder. *J.A.M.A.*, **77**:197, 1921.
942. JUDD, E. S. Surgical procedures in jaundiced patients. *J.A.M.A.*, **85**:88-92, 1925.
943. JUDD, E. S. Stricture of the common bile duct. *Ann. Surg.*, **84**:404-10, 1926.
944. JUDD, E. S. The relationship between changes in the liver and diseases in the biliary tract. *Collected Papers of the Mayo Clinic and the Mayo Foundation*, **23**:241-46, 1931.
945. JUDD, E. S., and BEAVER, D. C. Acute and subacute atrophy of the liver and the evolution of toxic cirrhosis. *Arch. Surg.*, **24**:775-97, 1932.

946. JUDD, E. S., and BURDEN, V. G. Benign stricture of the bile ducts. *Arch. Surg.*, **11**:459-72, 1925.
947. JUDD, E. S., and BURDEN, V. G. Internal biliary fistula. *Ann. Surg.*, **81**:305-12, 1925. Also *Collected Papers of the Mayo Clinic and the Mayo Foundation*, **16**:169-78, 1924.
948. JUDD, E. S., and BURDEN, V. G. Obstructive jaundice. *Am. J. M. Sc.*, **169**:888-96, 1925.
949. JUDD, E. S., and COUNSELLER, V. S. The effects of obstructive lesions of the common duct of the liver. *J.A.M.A.*, **89**:1751-56, 1927.
950. JUDD, E. S., and DRY, T. J. The significance of iron and copper in the bile of man. *J. Lab. & Clin. Med.*, **20**:609-15, 1935.
951. JUDD, E. S., and LYONS, J. H. White bile in the common duct. *Ann. Surg.*, **77**:281-92, 1923.
952. JUDD, E. S.; MENTZER, S. H.; and PARKHILL, E. A bacteriologic study of gallbladders removed at operation. *Am. J. M. Sc.*, **173**:16-23, 1927.
953. JUDD, E. S.; NICKEL, A. C.; and WELLBROCK, W. L. A. The association of the liver in disease of the biliary tract. *Collected Papers of the Mayo Clinic and the Mayo Foundation*, **22**:85-90, 1930.
954. JUDD, E. S.; SNELL, A. M.; and HOERNER, M. T. Transfusion for jaundiced patients. *J.A.M.A.*, **105**:1653-58, 1935.
955. JUDD, E. S., and WHITE, R. B. Prolonged drainage of the common duct. *Collected Papers of the Mayo Clinic and the Mayo Foundation*, **20**:144-51, 1928. *Ann. Surg.*, **90**:1035-45, 1929.
956. JUNG, F. T. Effects of ligating bile duct in rat. *Proc. Soc. Exper. Biol. & Med.*, **27**:362-64, 1930.
957. JURASZ, A. Untersuchungen über die Einwirkung der Galle und der Gallensäuren auf die Blutkörperchen. *Inaug. Diss. Greifswald*, F. Hache, 1871. Pp. 29.
958. KAEWEL, R., and KÜHN, R. Gibt es bakterizid wirkende Mittel, welche in die Gallenblase ausgeschieden werden? *Arch. f. d. ges. exper. Path.*, **125**:242-50, 1927.
959. KALK, H., and BRANISTEANU. Untersuchungen über die Wirkung einiger Pharmaka auf den Gallenfluss. *Arch. f. exper. Path. u. Pharmakol.*, **166**:555-69, 1932.
960. KALLMEYER, B. Über die Entstehung der Gallensäuren und die Beteiligung der Leberzellen bei diesem Process. *Diss. Dorpat*, 1889. Pp. 28.
961. KANASAKI, K. On the tissue respiration of the liver and spleen in cases of obstructive jaundice. *Jap. J. Gastroenterol.*, **4**:1-8, 1932.
962. KANASAKI, K. Effect of the injection of glucose upon the green bile. *Jap. J. Gastroenterol.*, **5**:91-100, 1933.

963. KANZLER, R. Enthält menschliche Galle Phagen? *Klin. Wchnschr.*, 11:2030-31, 1932.
964. KAPLAN, P. M. [Effect of muscular work on bile excreting function of the liver.] *Eksper. med. (Kharkov)*, 1935, pp. 55-64.
965. KAPSINOW, R.; ENGLE, L. P.; and HARVEY, S. C. Intra-abdominal biliary exclusion from the intestines-cholecyst-nephrostomy, a new method. *Surg. Gynec. Obst.*, 39:62-65, 1924.
966. KAPSINOW, R. The experimental production of duodenal ulcer by exclusion of bile from the intestines. *Ann. Surg., Phila.*, 83:614-17, 1926.
967. KARASAWA, R. Beiträge zur Bildung der Desoxybiliansäure aus Biliansäure und Desoxycholsäure und der Isodesoxybiliansäure aus Isobiliansäure und Desoxycholsäure. *J. Biochem.*, 5:105-12, 1925.
968. KARASAWA, R. Über den Einfluss der Gallensäuren auf den Eiweissstoffwechsel bei Keimdrüsen und über die Bedeutung der Choleinsäure. *J. Biochem.*, 6:139-43, 1926.
969. KARASAWA, R. Beziehung zwischen Aminosäuren und Gallensäuren bei der Fettverdauung im Darm. *J. Biochem.*, 7:117-27, 1927.
970. KARASAWA, R. Über den Einfluss der Gallensäuren auf den Eiweissstoffwechsel B.Z.W. Purinstoffwechsel und über die Bedeutung der Choleinsäure. *J. Biochem.*, 7:145-59, 1927.
971. KARASAWA, R., and SHODA, M. Über das Verhalten der Gallensäuren bei der Eiweissverdauung. *J. Biochem.*, 7:129-43, 1927.
972. KARATYGIN, V. M., and GEFTER, A. I. Über Veränderungen der Alkalireserve und des Zuckergehalts in der Galle bei Einwirkung von verschiedenen physiologischen Reizmitteln. *Ztschr. f. d. ges. exper. Med.*, 70:666-82, 1930; 86:697-708, 1933.
973. KARSNER, H. T. *Human pathology*, p. 35. Philadelphia: J. B. Lippincott Co., 1926.
974. KATAYAMA, I. Bile acids in jaundice. *Arch. Int. Med.*, 42:916, 1928.
975. KATZ, G., and LEFFKOWITZ, M. Die Blutkörperchensenkung, *Ergebn. d. inn. Med. u. Kinderh.*, 33:266-392, 1928.
976. KATZ, G., and RADT, P. Die Blutkörperchensenkung beim Ikterus. *Med. Klin.*, 23:760-61, 1927.
977. KAUFMANN, M. Contribution à l'étude de ferment glycosique du foie. *Compt. rend. Soc. de biol.*, 41:600-603, 1889.
978. KAUFTHEIL, L., and NEUBAUER, E. Vergleichende Untersuchungen über die bakterizide Kraft verschiedener Gallensäuren. *Klin. Wchnschr.*, 36:1623, 1924.
979. KAUFTHEIL, L., and NEUBAUER, E. Über Natriumdehydrocholati-diurese. *Arch. f. exper. Path. u. Pharmacol.*, 166:675-92, 1932.
980. KAWADA, Y. Der Einfluss der Gallensäure auf die Salzausscheidung in der Lebergalle. *J. Biochem.*, 13:133-44, 1931.

981. KAWADA, Y. Der Einfluss der Gallensäure auf die Salzausscheidung in der Lebergalle. *J. Biochem.*, 20:43-50, 1934.
982. KAWADA, Y. Über die Alkalienausscheidung in der Galle. *J. Biochem.*, 20:51-58, 1934.
983. KAWADA, Y. Einfluss der Gallensäure auf die Salzausscheidung in der Lebergalle. *Arbeit. Med. Fak. Okayama*, 4:196-205, 1934.
984. KAWADA, Y. Einfluss der Gallensäure auf die Ammoniakausfuhr im Harn. *J. Biochem.*, 21:213-18, 1935.
985. KAWAKATSU, R. Experimental studies on the influence of the seasons upon the pigment excreting function of the liver. *Jap. J. Gastroenterol.*, 8:80-92, 1936.
986. KAYA, S. On the change in the gastric function in the case of impaired function of the liver and kidneys. *Jap. J. Gastroenterol.*, 6:13-41, 1934.
987. KAZIRO, K. Über die antiseptische Wirkung der Gallensäuren im Kaninchendarm. *J. Biochem.*, 7:293-310, 1927.
988. KAZIRO, K., and TAKU, A. Über den Einfluss des Adrenalins und der Cholsäure auf die Kreatininausscheidung. *J. Biochem.*, 11:203-17, 1929.
989. KAZIRO, K., and TSUJI, K. Beiträge zur pankreaslipasefordernden Wirkung der Gallensäure und zu ihrer hämolytischen Wirkung. *J. Biochem.*, 11:333-43, 1930.
990. KAZUNO, T., and YAMAZAKI, K. Über Taurocholsäure. *Ztschr. f. physiol. Chem.*, 224:160-62, 1934.
991. KEHRER, E. Die Bedeutung des Ikterus in der Schwangerschaft für Mutter und Kind. Klinische und experimentelle Untersuchungen. *Arch. f. Gynäk.*, 81:129-59, 1907.
992. KEHRER, E. Der Einfluss der Galle auf die Uterusbewegungen. *Arch. f. Gynäk.*, 84:687-94, 1908.
993. KELLER, R. Zur Elektrochemie der Leber und Galle. *Biochem. Ztschr.*, 257:78-85, 1933.
994. KEMARSKY, W. Über die Einwirkung gallensäurer Salze auf Thiere. (Original in Russian.) Jahresberichte u. d. Fortschr. d. Anat. u. Physiol., 4:170-72, 1875.
995. KERPPOLA, W., and LEIKOLA, E. Zur Chemie des Bilirubins. *Skandin. Arch. f. Physiol.*, 54:120-26, 1928.
996. KERTI, F., and STENGEL, F. Über die Wirkung von Gallensubstanzen sowie Alkali und Säuren auf das Blutbild der weissen Maus. *Klin. Wchnschr.*, 9:2337-39, 1929.
997. KERTI, F., and STENGEL, F. Über die Einwirkung von gallensäuren Salzen auf das Blutbild der weissen Maus. *Ztschr. f. d. ges. exper. Med.*, 69:600-615, 1930.

998. KIKUZAWA, T. Antirachitische Wirkung der β -Cholsäure. *Ztschr. f. physiol. Chem.*, **220**:54-56, 1933.
999. KILLIAN, J. A. Interpretation of chemical analyses of blood and urine of cases exhibiting jaundice and disturbances of liver function. *Surg. Clin. N. Am.*, **12**:463-74, 1932.
1000. KIM, M. S., and IVY, A. C. Comparative value of "gastric mucin" and "alkalies" in prevention of "peptic" ulcer in biliary fistula dogs. *Proc. Soc. Exper. Biol. & Med.*, **29**:686-87, 1932.
1001. KIMURA, T. Über den Einfluss der Gallensäure auf den Phosphorstoffwechsel. *J. Biochem.*, **14**:51-60, 1931.
1002. KIMURA, S., and ISODA, I. On the acquisition of the antitoxic character of the liver. *Jap. J. Gastroenterol.*, **4**:298-303, 1932.
1003. KING, E. J., and ARMSTRONG, A. R. A convenient method for determining serum and bile phosphatase activity. *Canad. M. A. J.*, **31**:376-81, 1934.
1004. KING, J. H.; BIGELOW, J. E.; and PEARCE, L. Experimental obstructive jaundice. *J. Exper. Med.*, **14**:159-78, 1911.
1005. KING, J. H., and STEWART, H. A. Effect of the injection of bile on the circulation. *J. Exper. Med.*, **11**:673, 1909.
1006. KIPP, H. A. Observations on the variations in bile pressure in the human biliary tract. *J.A.M.A.*, **106**:2223-26, 1936.
1007. KIRIKOV, N. N. [Gastric digestion in icterus.] Russian. *Russ. vrač, St. Petersburg*, **5**:505-7, 542-44, 573-75, 1507-8, 1906.
1008. KIRKEGAARD, C. Etiology of bradycardia in jaundice. *Hospitaltid.*, **73**:767-71, 1930.
1009. KISHI, S. Untersuchung der Kaninchengalle. *Ztschr. f. physiol. Chem.*, **238**:210-20, 1936.
1010. KIZU, E. Einfluss der verschiedenen Bakteriengifte auf die Leberfunktion. *Jap. J. Gastroenterol.*, **5**:236-78, 1933.
1011. KLEE, H. Beziehungen der Hämolyse zur Gallensecretion. *Giessen*, 1908.
1012. KLEE, P., and KLÜPFEL, O. Experimenteller Beitrag zur Funktion der Gallenblase. *Mitt. a. d. Grenzgeb. der Med.*, **27**:785-95, 1914.
1013. KLING, D. H. Bilirubin in effusions of the joints. *Arch. Surg.*, **20**:17-25, 1930.
1014. KLODT, W. Über den Einfluss der Galle auf Vitamin-C Resorption. *Med. Welt*, **10**:477-78, 1936.
1015. KLOSE, H., and WACHSMUTH, W. Seltene chirurgische Erkrankungen des Gallensystems. *Arch. f. klin. Chir.*, **123**:1, 1923.
1016. KLUJEW, N. G. Über den Einfluss der Galle auf die Agglutinabilität von atypischen Paratyphusbakterien. *Zentralbl. f. Bakt.*, **120**:34-40, 1931.

1017. KNICK, A., and PRINGSHEIM, J. Beiträge zur Frage der inneren Desinfection. Über antiseptische Beeinflussung der Galle durch innere Anwendung von Desinficientien. *Deutsches Arch. f. klin. Med.*, 101:137-49, 1910.
1018. KNOEPFELMACHER, W. Das Ausrystallisiren des Bilirubins im Fettgewebe. *Wien. klin. Wchnschr.*, 9:522, 1896.
1019. KOBAYASHI, TODI. Über die Pentosuria bei experimentellem Stauungsikterus und bei subcutaner Zufuhr der Gallensäuren beim Kaninchen. *J. Biochem.*, 9:251-60, 1928.
1020. KOBES, J. J. Antagonistic action of sugar to bile salts in blood coagulation. *Med. Bull. Univ. Cincinnati*, 6:102-9, 1931.
1021. KOCHMANN, M. Pharmakologie der Verdauungsdrüsen. *Leber. Handbuch der normalen und pathologischen Physiologie*, 3:1441-66, 1927.
1022. KOIMAI, H. Experimentelle Untersuchungen über die Giftigkeit der Galle. *Fukuoka-Ikwadaigaku-Zasshi*, 22:105, 1929.
1023. KOSSEL, A. Zur Kenntniss der Galle. *Verhandl. d. Ver. f. inn. Med.*, 8:78-86, 1888-89.
1024. KOSSEL, A. Zur Kenntniss des Gallenfarbstoffs. *Ztschr. f. physiol. Chem.*, 161:1-16, 1926.
1025. KOSTER, H.; SHAPIRO, A.; and LERNER, H. On the rate of secretion of bile. *Am. J. Physiol.*, 115:23-26, 1936.
1026. KOTTMEIER, J. F. Zur Kenntniss der Leber. *Diss. Inaug. Würzburg: J. C. Becker*, 1857. Pp. 50.
1027. KOZLOWSKI, A. Comparative studies of the action on the pneumococcus of bile acids and unsaturated fatty acids, found in bile in the form of soaps. *J. Exper. Med.*, 42:453, 1925.
1028. KRAMER, P. H. Researches in icterus neonatorum. *Nederl. Tijdschr. v. Geneesk.*, 1:249-63, 1926.
1029. KRAUSCH, W. Der Hydrops des gesamten Gallensystems bei chronischem Choledochusverschluss und seine Bedeutung für den Chirurgen. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 23:138-68, 1911.
1030. KRIEG, E. G. Hepatic trauma. *Arch. Surg.*, 32:907-14, 1936.
1031. KRILOFF, D. O. [Elimination of bile through the respiratory organs.] Russian. *Izviest. Imp. Voenno-med. Akad. St. Petersburg*, 22:587-600, 1911.
1032. KRUMBHAAR, E. B. Recent changes in conception of jaundice. *Atlantic M. J.*, 24:140-42, 1925.
1033. KÜFFRATH, D. Über die Abwesenheit der Gallensäuren im Blute nach dem Verschluss der Gallen- und des Milchbrustganges. *Du Bois-Reymond Arch. f. Physiol.*, 1880, pp. 92-94.
1034. KUHN, W. Beiträge zur Lehre vom Icterus. *Virchows Arch. f. path. Anat.*, 14:310-56, 1858.

1035. KÜHNE, W. Über directe und indirecte Muskelreizung mittelst chemischer Agentien. Arch. f. Anat., Physiol. M. Wissensch. Med., Abteil, 1859, p. 213; 1860, p. 315.
1036. KUNDE, FELIX. De hepatitis ranarum extirpatione. Dissert. Inaug. Berlin, 1850.
1037. KUNKEL, A. J. Über das Verhältniss der mit dem Eiweiss verzehrten zu der durch die Galle ausgeschiedenen Schwefelmenge. Arb. a. d. physiol. Inst. z. Leipsic, 10:112-31, 1876.
1038. KURAMOTO, T. Einfluss der Gallensäure auf die Wasserstoffionenkonzentration des Harns. J. Biochem., 19:245-48, 1934.
1039. KURAMOTO, T. Beiträge zur Kenntniss der Glykogenbildung der Leber durch Gallensäure. J. Biochem., 19:315-18, 1934.
1040. KURAMOTO, T. Einfluss der Cholsäure auf den pH und die Phosphatausscheidung im Darmsaft. J. Biochem., 19:425-36, 1934.
1041. KURAMOTO, T. Einfluss der Cholsäure auf die Ausscheidung von Na, K, Ca, und Mg im Darmsaft. J. Biochem., 19:437-48, 1934.
1042. KÜRTEH, H. Die Senkungsgeschwindigkeit der roten Blutkörperchen in ihrer Beziehung zu Cholesterin und Lecithin. Arch. f. d. ges. Physiol., 185:248-61, 1920.
1043. KUSAKA, S. Influence of bile acid salts upon amounts of sugar and cholesterol-bodies in the blood. Jap. J. Gastroenterol., 4:196-201, 1932.
1044. KUSAKA, S. Influence of fat-soluble vitamin upon the amounts of cholesterol bodies in the bile in rabbits. Jap. J. Gastroenterol., 5:31-35, 1933.
1045. KÜSTER, W. Beiträge zur Kenntniss der Gallenfarbstoffe. Ztschr. f. physiol. Chem., 26:314-37, 1898-99.
1046. KÜSTER, W. Über die Aufarbeitung von Rindergallensteinen. Abderhalden, Biologische Arbeitsmethoden, Abt. 1, 8.
1047. KÜSTER, W. Beiträge zur Kenntniss der Gallenfarbstoffe. Ztschr. f. physiol. Chem., 59:63-95, 1909.
1048. KÜSTER, W., and HAAS, R. Über die Aufarbeitung von Rindergallensteinen. Über Gallenfarbstoffe. Ztschr. f. physiol. Chem., 141:279-81, 1924.
1049. KUSUI, K. Beiträge zur Bestimmung der Blutgallensäuren. J. Biochem., 18:345-68, 1933.
1050. KUWASHIMA, K. Studies on some factors in the coagulation of blood. J. Biochem., 3:91-147, 1924.
1051. LABBÉ, M.; BOULIN, R.; and PETRESCO, M. La Diabète bronzé. Ann. de méd., 37:5-39, 1935.
1052. LABES, R., and SCHLENKERT, T. Über das Verhalten von disoxycholsäuren Natrium und Saponin gegenüber Membranen und Gewebestandteilen. Arch. f. exper. Path. u. Pharmacol., 166:186-204, 1932.

1053. LABORDE, J. B. V. *Physiologie pathologique de l'ictère*. Thèse. Paris, 1869.
1054. LABROSSE, R. *Contribution à l'étude du cholépéritoine spontané*. Lyon, 1912.
1055. LADD, W. E. Congenital atresia and stenosis of the bile ducts. *J.A.M.A.*, 91:1082-85, 1928.
1056. LAGANE, L. Action de la bile "in vitro" sur le développement des microbes de l'intestin. *Comp. rend. Soc. de biol.*, 73:242-43, 1912.
1057. LAKE, N. C., and PETTERSON, J. White bile. *Lancet*, 2:753-55, 1934.
1058. LANDAU, A. [Experimental study of cholaemia.] *Polish. Gas. lek.*, 24:339-44, 379-84, 1904.
1059. LANDAU, A. Experimentelles zur Cholämie. *Deutsches Arch. f. klin. Med.*, 79:551-62, 1904.
1060. LANDAU, A., and HELD, J. Sur les états morbides avec hypobilirubinémie. *Soc. méd. d. hôp. de Paris*, 50:637-39, 1926.
1061. LANDOIS, L. Über den Einfluss der Galle auf die Herzbewegung. *Deutsche Klin.*, 46:449, 1863. Résumé in *Centralbl. f. d. med. Wissensch.*, Dec. 5, 1863.
1062. LANG, C., and JUNGSMANN, H. Über die Wirkung von Gallensäure auf Zucker und Cholesteringehalt im Blute. *Klin. Wchnschr.*, 6:2241-42, 1927.
1063. LANG, K., and LUEKEN, B. Eine titrimetrische Mikromethode zur Bestimmung der Cholsäure in der Galle. *Biochem. Ztschr.*, 273:446-51, 1934.
1064. LANG, S. Beiträge zur Lehre vom Icterus. *Ztschr. exp. Path. u. Ther.*, 3:473-75, 1906.
1065. LANGHELD, K. Über die Bestandteile der Rindergalle. *Ber. d. deutsch. chem. Gesellsch.*, 41:378, 1908.
1066. LANGLEY, W. D.; ROSENBAUM, M. G.; and ROSENBAUM, M. M. The solubility of calcium stearate in solutions containing bile and in water. *J. Biol. Chem.* 99:271-78, 1932.
1067. LAROCHE, G., and FLANDIN, C. Recherche histologique de la cholestérine dans la bile et les parois de la vésicule biliaire. *Compt. rend. Soc. de biol.*, 72:660-61, 1912.
1068. LA ROSA, G. L'Action de la bile sur le bacille de la peste. *Soc. internaz. di microbiol. Boll. d. sez ital.*, 2:488-90, 1930.
1069. LA ROSA, G. L'azione della bile sul bacillo della peste. *Gior. di batteriol. e immunol.*, 5:1768-80, 1930.
1070. LASSAR-COHN. Die Säuren der menschlichen Galle. *Ztschr. f. physiol. Chem.*, 19:563-73, 1894.
1071. LASSAR-COHN. Die Säuren der Rindergalle und der Menschengalle. Hamburg and Leipzig, 1898.

1072. LATSCHINOFF, P. Über eine der Cholsäure analoge neue Säure. Ber. deutsch. chem. Gesellsch., Berlin, 18:3039-47, 1885.
1073. LAUGIER, MAURICE. Des hémorrhagies liées au rétrécissement et à l'occlusion des voies biliaires. Paris, 1870. Pp. 30.
1074. LAVERAN, A., and TEISSIER, J. Nouveaux éléments de pathologie et de clinique médicales, 2:738, 1879.
1075. LAWEN, A., and DITTLER, R. Untersuchungen über die Wirkung von Bakterien Toxinen sowie von Blut, Fruchtwasser, Harn, Galle und Pankreassaft auf den isolierten Dünndarm. Ztschr. f. d. ges. exper. Med., 3:1, 1914.
1076. LEBERMANN, F. Über die diuretische Wirkung der Gallensäuren. Deutsche med. Wchnschr., 53:2020-22, 1927.
1077. LEE, R. I., and VINCENT, B. The relation of calcium to the delayed coagulation of blood in obstructive jaundice. Arch. Int. Med., 16:59-66, 1915.
1078. LEE, R. I., and WHITE, P. D. A clinical study of the coagulation time of blood. Am. J. M. Sc., 145:495-503, 1913.
1079. LEGG, J. W. On the changes in the liver which follow ligature of the bile ducts. St. Bartholomew's Hosp. Rep., 9:161-81, 1873.
1080. LEGG, J. An inquiry into the cause of the slow pulse in jaundice. Proc. Roy. Soc., 24:442-48, 1875-76.
1081. LEGG, J. W. The urea and chlorides in the urine of jaundice. Medico-Chir. Trans., London, 59:149-63, 1876.
1082. *LEGG, JOHN WICKHAM. On the bile, jaundice, and bilious diseases. New York: D. Appleton & Co., 1880.
1083. LEISCHNER, A. W. Therapeutische Versuche bei Melancholie, Schizophrenie und Migräne. Med. Klin., 26:1592-96, 1930.
1084. LEITES, S., and ISABOLINSKAJA, R. Veränderungen des Gallenchemismus und der Gallensekretion unter dem Einfluss einiger Inkrete und vegetativen Gifte. Arch. f. exper. Path. u. Pharmacol., 170:592-608, 1933.
1085. LEITES, S., and JUSSIN, W. Veränderungen des Gallenchemismus und der Gallensekretion bei alimentären Belastungen. Arch. f. exper. Path. u. Pharmacol., 160:365-84, 1933.
1086. LEITES, S., and KOSŁOWA, A. Veränderungen des Calcium- und Kaliumgehaltes der Galle nach alimentären Belastungen. Arch. f. exper. Path. u. Pharmacol., 169:385-91, 1933.
1087. LEJARS, F. Chirurgie d'urgence, p. 340. 8th ed. Paris: Masson et Cie, 1921.
1088. LEMBERG, R. Bile pigments. Biliverdin, uteroverdin and oocyan. Biochem. J., 28:978-87, 1934.
1089. LEMBERG, R. Transformation of haemins into bile pigments. Biochem. J., 29:1322-36, 1935.

1090. LEMBERG, R., and WYNDHAM, R. A. Reduction of biliverdin to bilirubin in tissues. *Biochem. J.*, 30:1147-70, 1936.
1091. LEMIERRE, A.; BRULÉ, M.; WEILL; and LORDAT. L'Examen chimique et ultramicroscopique du sang dans l'étude de l'absorption intestinale des graisses. *Bull. Soc. méd. des hôp.*, 1913, p. 72.
1092. LEMIERRE, A.; BRULÉ, M.; and GARBAN. Les Retentions biliaires par lésions de la cellule hépatique. *Semaine méd.*, 34:301, 1914.
1093. LEMMEL, G. Die physiologische Gallenstase in ihrer Beziehung zur Gallensteinbildung. *München. med. Wchnschr.*, 80:380-82, 1933.
1094. LE NOIR, R. C., and JACQUELIN, A. Ulcus gastrique et néphrite latentes. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 44:1402-6, 1920.
1095. LEPEHNE, G. Blutveränderungen bei experimentellem Choledochusverschluss. *Königsberg*, 1911.
1096. LEPEHNE, G. Untersuchungen über Gallenfarbstoff im Blutserum des Menschen. *Deutsches Arch. klin. Med.*, 132:96, 1920; 135:79, 1921.
1097. *LEPEHNE, G. Pathogenese des Ikterus. *Ergebn. d. inn. Med. u. Kinderh.*, 20:221-80, 1921.
1098. LEPEHNE, G. Experimentelle Untersuchungen zum mechanischen und dynamischen Ikterus. *Deutsches Arch. f. klin. Med.*, 136:88, 1921.
1099. LEPEHNE, G. Vergleichende Untersuchungen über den Bilirubin und Gallensäurestoffwechsel beim Lebergesunden, Leberkranken und Neugeborenen. *Klin. Wchnschr.*, 41:2031, 1922.
1100. LEPEHNE, G. Über Leberfunktionsprüfungen. *München. med. Wchnschr.*, 69:342-44, 1922.
1101. LEPINE, R. Sur la résorption eventuelle de la bile par le réseau veineux sus-hépatique. *Compt. rend. Soc. de biol.*, 3:998, 1896.
1102. LEREBoulLET, P. Comment expliquer l'ictère simple du nouveau-né? *Paris méd.*, 69:384-88, 1928.
1103. LÉTIENNE, A. De la bile à l'état pathologique. Thèse. Paris, 1891.
1104. LEYDEN, E. *Leberkrankheiten*. Berlin, 1861.
1105. LEYDEN, E. *Beiträge zur Pathologie des Icterus*. Berlin: A. Hirschwald, 1866. Pp. 210.
1106. LICHT, H. Untersuchungen über den Einfluss der Bakterien auf die Gallensäuren. *Biochem. Ztschr.*, 153:159-64, 1924.
1107. LICHTMAN, S. S. A new procedure for the estimation of bile salts in body fluids based on bile salt hemolysis. *J. Biol. Chem.*, 107:717-30, 1934.
1108. LICHTMAN, S. S. The blood clearance and renal excretion of bile acids following the intravenous injection of cholic and desoxycholic acids. *Am. J. Physiol.*, 117:665-71, 1936.
1109. LICHTMAN, S. S., and STERN, E. L. Influence of bile salts on the nervous system following intraspinal usage. *Proc. Soc. Exper. Biol. & Med.*, 22:1201-4, 1925.

1110. LICHTWITZ, L. Experimentelle Untersuchungen über die Bildung von Niederschlägen in der Galle. *Deutsches Arch. f. klin. Med.*, 92: 100-108, 1907.
1111. LICHTWITZ, L. Über die Bedeutung der Kolloide für die Konkrementbildung und die Verkalkung. *Deutsche med. Wchnschr.*, 36: 704-6, 1910.
1112. LICHTWITZ, L. Prinzipien der Konkrementbildung. *Handbuch der normalen und pathologischen Physiologie*, 4: 598-665, 1929.
1113. LIFSHITZ, L. S. Veränderungen des Gallencholesterins und der Gallensäuren bei einigen Lebererkrankungen. *Wien. Arch. f. inn. Med.*, 29: 259-70, 1936.
1114. LIFSCHÜTZ, J. Zur Kenntnis der Cholsäure und deren Ursprung. *Ber. d. deutsch. chem. Gesellschaft.*, 47: 1459-60, 1914.
1115. LILIENTHAL, H. Chronic biliary fistula. *Ann. Surg.*, 67: 765-66, 1923.
1116. LIMBOURG, P. Über die antiseptische Wirkung der Gallensäuren. *Ztschr. f. physiol. Chem.*, 13: 196-201, 1889.
1117. LINTON, R. R. The sedimentation rate of blood as an index of the haemorrhagic tendency in obstructive jaundice. *Ann. Surg.*, 91: 694-704, 1930.
1118. LINTON, R. R. The relation of calcium to the haemorrhagic tendency in obstructive jaundice. *Ann. Surg.*, 93: 707, 1931.
1119. LINTON, R. R. The relation of the blood fibrin to the haemorrhagic diathesis of obstructive jaundice. *Ann. Surg.*, 96: 394-405, 1932.
1120. LISZYNSKI, J. *Consideratio bilis physiologica et pathologica*. Bero lini, 1863.
1121. LOEBISCH, W. F., and FISCHLER, M. Über einen neuen Farbstoff in der Rindergalle (Bilipurpurin). *Wien. Mon. Hefte. Chem.*, 24: 335-50, 1903.
1122. LOEFFLER, K. Über Beziehungen der Gallensäuren zum Nahrungscholesterin. *Ztschr. f. physiol. Chem.*, 178: 186-91, 1928.
1123. LÖPER, M.; LEMAIRE, A.; and TAUZIN, J. Action expérimentale des hormones femelles sur la bile et sur l'intestin. *Compt. rend. Soc. de biol.*, 116: 482-84, 1934.
1124. LOEVENHART, A. S., and SOUDER, C. G. On the effect of bile upon the hydrolysis of esters by pancreatic juice. *J. Biol. Chem.*, 2: 415-25, 1907.
1125. LOEWENSTON, A. Experimentelle Untersuchungen über den Einfluss einiger Abführmittel und der Clysmata auf Secretion und Zusammensetzung der Galle, sowie deren Wirkung bei Gallenabwesenheit im Darm. *Dorpat*, 1891.
1126. LÉWY, G. Expériences sur la production d'ulcères duodénaux par dérivation isolée de la bile. *Bull. et mém. Soc. de chir.*, 56: 243-49, 1888.

1127. LÆWY, G. Production expérimentale d'ulcères duodénaux par dérivation isolée de la bile. *Bull. et mém. Soc. de chir.*, 57:739-52, 1931.
1128. LÆWY, G. Influence de la déperdition de bile sur quelques éléments du sang. *Compt. rend. Soc. de biol.*, 119:178-79, 1935.
1129. LÆWY, G. Recherches expérimentales sur le pH du contenu duodénal en l'absence de bile. *Compt. rend. Soc. de biol.*, 119:382-84, 1935.
1130. LOGAN, J. F. The protein matter of bile. *J. Biol. Chem.*, 58:17-32, 1923.
1131. LONDON, E. S. Angiostomie u. Organestoffwechsel. Monograph. Moscow: Des All-Union-instituts für exper. Med., 1935. Pp. 206.
1132. LONDON, E. S., and KRYZANOWSKAJA, L. J. Der Ort der Bilirubinbildung nach Versuchen an angiostomierten Hunden. *Ztschr. f. physiol. Chem.*, 227:229, 1934.
1133. LONG, J. H., and GEPHART, F. On the behavior of lecithin with bile salts, and the occurrence of lecithin in bile. *J. Am. Chem. Soc.*, 30:1312-18, 1908.
1134. LONG, J. H., and JOHNSON, W. A. The purity of commercial bile salts. *J.A.M.A.*, 53:1412-14, 1909.
1135. LÖWIT, M. Über den Einfluss der Gallensäuren-Salze auf die Herz-tätigkeit sowie auf einige Funktionen der peripheren und zentralen Nervensubstanzen. *Ztschr. f. Heilk.*, 2:459-96, 1882.
1136. LUCILIUS, C. ENNIUS. Nonius Marcellus 445, 18.
1137. LUCKE, H. Beiträge zur Physiologie und Pathologie des menschlichen Harnsäurestoffwechsels; der Harnsäuregehalt der Galle in der Norm und bei Erkrankungen der Gallenwege. *Ztschr. f. d. ges. exper. Med.*, 72:753-59, 1930.
1138. LUCKE, H., and FREY, J. Die Größenordnung der Stickstoff-ausscheidung über die Gallenwege. *Ztschr. f. d. ges. exper. Med.*, 86:1-11, 1933.
1139. LUCKE, H., and TAAKS, G. Die Stickstoffausscheidung in der Galle unter normalen und krankhaften Bedingungen. *Ztschr. f. d. ges. exp. Med.*, 79:234-42, 1931.
1140. LÜDKE, H. Über die Hämolyse durch Galle und die Gewinnung von die Gallenhämolyse hemmenden Serum. *Centr. f. Bakt.*, 1 te Abt., Orig., 42:455-62, 552-61, 1906.
1141. LUGLI, A. La Tossicità della bile avanti e dopo la legatura della vena porta. *Biol. d. Accad. med. d. Roma*, 21:fasc. vii-viii, 1895.
1142. LUGLI, A. La Tossicità della bile prima e dopo la legatura della vena porta. *Istituto di farmacologia sperimentale*, 3:229-311, 1896.
1143. LUGLI, A. Die Toxici-tät der Galle vor und nach der Ligatur der Vena Portae. *Untersuchungen zur Naturlehre des Menschen*, 16:295-383, 1899.

1144. LUNDBERG, H. Bile flow and bile pigment output after denervation of liver. *Am. J. Physiol.*, **97**:602-4, 1931.
1145. LURJE, H. S. Zur Frage über die Wirkung der Galle auf die Dickdarmbewegungen. *Arch. Verdauungskr.*, **36**:No. 5-6, 429-32, 1926.
1146. LUTKENS, U. Aufbau und Funktion der hepatischen Gallewege. Leipzig: F. C. W. Vogel, 1926. Pp. 205.
1147. LYON, B. B. V. The bacteriology of bile obtained by duodenal tube biliary drainage. *J. Lab. & Clin. Med.*, **17**:583-94, 1932.
1148. LYON, B. B. V., and SWALM, W. A. The therapeutic value of non-surgical drainage of the biliary tract. *J.A.M.A.*, **85**:1541-48, 1925.
1149. LYON, B. B. V.; SWALM, W. A.; BARTLE, H. J.; and STERNER, R. F. The therapeutic effectiveness of dehydrocholic acid in liver and biliary tract disease. *M. Rec.*, **139**:123-28, 1934.
1150. LYON-CAEN, LOUIS. La Tension superficielle: son application à la différenciation des choluries et à l'étude du rôle du foie dans les ictérus. Thèse. Paris: G. Steinheil, 1910.
1151. LYON-CAEN, L. Action de la bile et des sels biliaires sur l'excitabilité neuromusculaire. *Compt. rend. Soc. de biol.*, **93**:237-40, 1925.
1152. LYON-CAEN, L. Action de la bile et des sels biliaires sur l'excitabilité et la conductibilité cardiaques. *Compt. rend. Soc. de biol.*, **97**:216-17, 1927.
1153. MACHIDA, H. Experimentelle Untersuchungen über die Resorption der Gallenbestandteile vom Darm aus und über die Abfuhrwege derselben in die Blutbahn bei der Entstehung verschiedener Ikterusarten. *Nagasaki Igakkwai Zassi*, **14**:1268-72, 1936.
1154. MACHT, D. I. The behavior of rats after the injection of bile salts, urea, creatin, creatinin. *J. Pharmacol. & Exper. Ther.*, **22**:117-22, 1923-24.
1155. MACHT, D. I.; GROLLMAN, A.; and HYNDMAN, O. R. Relation between chemical structure of bile acids and their effects on animal and plant tissues. *Am. J. Physiol.*, **68**:141, 1924.
1156. MACHT, D. I., and HYNDMAN, O. R. The relation between the chemical structures of bile acids and their phytopharmacological and zoopharmacological reactions. *J. Pharmacol. & Exper. Therap.*, **22**:483-90, 1923.
1157. MACKAY, J. C. H. Beiträge zur Lehre des Icterus. *Arch. f. exper. Path. u. Pharmacol.*, **19**:269-89, 1885.
1158. MACKENZIE, J. A study of the pulse. London: Macmillan Co., 1902.
1159. MACLAREN, A. Perforation of the gallbladder. *Tr. Am. Surg. A.*, **23**:206-21, 1905.
1160. MACLEAN, H., and HUTCHINSON, L. Observations on the haemolytic action of certain bile derivatives. *Biochem. J.*, **4**:369-84, 1909.

1161. MACLURG, J. Experiments on the human bile and reflections on the biliary secretion. London, 1772.
1162. MACMUNN, C. A. Observations on the colouring-matters of the so-called bile of invertebrates; on those of the bile of vertebrates. *Proc. Roy. Soc. Lond.*, 35:370-403, 1883.
1163. MACMUNN, C. A. Observations on some of the colouring matters of the bile and urine. *J. Physiol.*, 6:29-39, 1885.
1164. MACNIDER, W. DE B. The resistance of fixed tissue cells morphologically altered through processes of repair. *Tr. A. Am. Phys.*, 49: 14-22, 1934.
1165. MAEDA, T. A contribution to the knowledge of the genesis of jaundice. *Jap. J. Gastroenterol.*, 4:26-40, 1932.
1166. MAGATH, T. B., and SHEARD, C. Spectrophotometric analysis of blood serum in normal and pathologic conditions. *Arch. Int. Med.*, 39:214-25, 1927.
1167. MAGENDIE, F. An elementary compendium of physiology, p. 388. E. MILLIGAN (tr.). Philadelphia: James Webster, 1824.
1168. MAGENDIE, F. *Précis élémentaire de physiologie*. 4th ed. Bruxelles: Adolph Wahlen et Compagne, 1836.
1169. MAGNER, W., and HUTCHESON, J. M. Cholecystitis: a bacteriological and experimental study. *Canad. M. A. J.*, 27:469-77, 1932.
1170. MAKIMURA, H. Studies of vitamins in bile. *Acta med. Keijo*, 12: 147-91, 1929.
1171. MAKINO, H. Über Tetraoxy-bufostan, einen vierwertigen Alkohol $C_{27}H_{48}O_8$ und Wintergalle von Kröten. *Ztschr. f. physiol. Chem.*, 220:49-54, 1933.
1172. MAKINO, H. Beiträge zur Kenntnis der Taurocholsäure aus Fischgalle. *J. Biochem.*, 19:249-51, 1934.
1173. MAKINO, H. Über den Einfluss des Thyroxins auf die hypoglykämische Wirkung der Cholsäure. *Arb. a. d. med. Fak. Okayama*, 4:461-64, 1935.
1174. MAKINO, H. Über die Wirkung der Trioxysterocholensäure auf die Pankreaslipase und auf das Blutkörperchen. *Arb. a. d. med. Fak. Okayama*, 4:508-11, 1935.
1175. MALAMUD, T. La Insulina en el prurito de los ictericos. *Prensa méd. argent.*, 17:1234-36, 1931.
1176. MALAMUD, T. El Prurito de los ictericos no es de origen colico. *Prensa méd. argent.*, 17:1402-4, 1931.
1177. *MALAY, R. Chemie der Galle. In L. HERMANN'S Handbuch der Physiologie, 5: Theil 2, 118-85. Leipsic, 1883.
1178. MALCOLM, J. D. Cholecyst-duodenostomy for acute emaciation following the formation of a biliary fistula. *Clin. J.*, 35:239, 1910.

1179. MALKOFF, G. [The pathology of icterus.] Russian. Inaugural dissertation. St. Petersburg, 1897.
1180. MALKOFF, G. Zur Pathologie des Ikterus. Über die Ausscheidung der Gallensäuren durch den Harn, die Bauchwassersucht und einige andere Erscheinungen bei der Gallenretention. Jahresb. ü. d. Fortschr. d. Tierchem., 27:785-87, 1897.
1181. MALLET-GUY, M. Pancréatites chroniques avec ictère. Thèse. de Lyon. Masson, 1925. Pp. 308.
1182. MALLET-GUY, P.; CHAMBON, M.; CHAMBON, A.; and CROIZAT, P. Les Variations physico-pathologiques du taux de la mucine dans le mucus biliaire; leur signification fonctionnelle. Compt. rend. Soc. de biol., 122:313-16, 1936.
1183. MANDELBAUM, M. Über die Wirkung von taurocholsäuren Natrium und tierischer Galle auf den Pneumococcus, Streptococcus mucosus und auf die andern Streptokokken. München. med. Wchnschr., 54: 1431-33, 1907.
1184. MANGELSDORF, J. Über biliäre Lebercirrhose. Deutsches Arch. f. klin. Med., 31:522, 1882.
1185. MANN, F. C. Study of toxicity of sphincter at duodenal end of common bile duct. J. Lab. & Clin. Med., 5:107, 1919.
1186. MANN, F. C. The functions of the gallbladder. Physiol. Rev., 4: 251-73, 1924.
1187. MANN, F. C. The extrahepatic formation of bilirubin. Ergebn. d. Physiol., 24:379-98, 1925.
1188. MANN, F. C. Modified physiologic processes following total removal of the liver. J.A.M.A., 85:1472-75, 1925.
1189. MANN, F. C., and BOLLMAN, J. L. Relation of the gallbladder to development of jaundice following obstruction of the common bile duct. J. Lab. & Clin. Med., 10:540-44, 1925.
1190. MANN, F. C., and BOLLMAN, J. L. Jaundice. J.A.M.A., 104:371-74, 1935.
1191. MANN, F. C.; BOLLMAN, J. L.; and MAGATH, T. B. The formation of bile pigment after total removal of the liver. Am. J. Physiol., 69: 393-409, 1924.
1192. MANN, F. C., and GIORDANO, A. S. The bile factor in pancreatitis. Arch. Surg., 6:1-30, 1923.
1193. MANN, F. C., and HIGGINS, G. M. Effect of pregnancy on the emptying of the gallbladder. Arch. Surg., 15:552-59, 1927.
1194. MANN, F. C.; SHEARD, C.; and BOLLMAN, J. L. The extrahepatic formation of bilirubin. Am. J. Physiol., 74:49-60, 1925.
1195. MANN, F. C.; SHEARD, C.; BOLLMAN, J. L.; and BALDES, E. J. The site of the formation of bilirubin. Am. J. Physiol., 74:497-510, 1925.

1196. MANN, F. C.; SHEARD, C.; BOLLMAN, J. L.; and BALDES, E. J. The formation of bile pigment from hemoglobin. *Am. J. Physiol.*, **76**: 306-13, 1926.
1197. MANTE, D., and HAGIESCO, D. Action des injections de sels biliaires sur le rythme du poulx chez le singe normal. *Compt. rend. Soc. de biol.*, **99**: 427, 1928.
1198. MANTA, I., and VANCEA, P. L'Influence des groupements fonctionnels des acides biliaires sur la pression artérielle et sur la respiration. *Compt. rend. Soc. de biol.*, **127**: 269-70, 1936.
1199. MANTA, I., and VANCEA, P. Beiträge zur Pharmakodynamie der Gallensäuren. Einfluss der Funktionsgruppen. Cardio-vaskuläre und Atmungswirkung. *Arch. f. exper. Path. u. Pharmakol.*, **180**: 631-38, 1936.
1200. MAREY, E. De l'uniformité du travail du cœur, lorsque cet organe n'est soumis à aucune influence nerveuse extérieure. *Compt. rend. Soc. de biol.*, **77**: 367, 1873.
1201. MAREY, E., and KLEINFETTER. Du poulx dans l'ictère simple. Thèse. Nancy, 1874.
1202. MARINELLI, F. Colecisti-gastrostomia e colecisti-enterostomia sperimentali. *Arch. ital. di chir.*, **13**: 343-71, 1925.
1203. MARINESCO, G., and MINEA, J. Lésions des centres nerveux produites par l'injection locale de bile. *Compt. rend. Soc. de biol.*, **64**: 417, 1908.
1204. MARINO, S., and FERRO-LUZZI, G. Ricerche sperimentali sull'azione del glicocolato e taurocolato sodico sul cuore di rana. *Arch. di farmacol. sper.*, **58**: 270-79, 1934.
1205. MARSHALL, J. Über die Hufner'sche Reaction bei amerikanischer Ochsen-galle. *Ztschr. f. physiol. Chem.*, **11**: 233-38, 1888.
1206. MARSSON, T. Composition of the bile of the goose. *Chemist, N.S.*, **1**: 64, 1849-50.
1207. MARTIN, L. Jaundice. Methods of diagnosis and treatment of its causes. *Bull. Johns Hopkins Hosp.*, **59**: 78-98, 1936.
1208. MARTON, I., and MOLNÁR, B. E. [Sugar content of human bile.] *Orvosi hetil.*, **76**: 9-10, 1932.
1209. MARUNO, Y. Experimental studies on the halogen-excretion from the liver. Studies on the chlorine-excreting portion of the liver. *Jap. J. Gastroenterol.*, **2**: 231-38, 1930.
1210. MARUNO, Y. Experimental studies on the halogen-excretion from the liver. The significance of the liver and the kidneys in the chlorine-excretion. *Jap. J. Gastroenterol.*, **3**: 60-66, 1931.
1211. MARUNO, Y. On the excretion of bromine and iodine from the liver. *Jap. J. Gastroenterol.*, **3**: 97-118, 1931.

1212. MARX, A. V., and HENPKE, W. Über die Giftigkeit des Harns. *Ztschr. f. exper. Med.*, 62:724-38, 1928.
1213. MASON, E. C., and NAV, C. A. The cause of death due to liver autolysis. *Surg. Gynec. Obst.*, 60:769-74, 1935.
1214. MASTROSIOMONE, F. La Cisticogastrostomia. *Semana méd.*, 28: 193-200, 1921.
1215. MATHESON, A., and TUMPEER, I. H. Congenital atresia of the bile ducts. *Am. J. Dis. Child.*, 40:571-80, 1930.
1216. MATHEWS, A. P. *Physiological chemistry*. 3d ed. New York: Wm. Wood & Co., 1921.
1217. MATHIEU, M., and LUCCIONI, F. Pathogénie et traitement des "biles noires." *Marseille-méd.*, 2:589-99, 1934.
1218. MATSUDA, T. Experimental investigation into the appearance of protein in bile. *Jap. J. Gastroenterol.*, 2:130-47, 1930; 3:14-37, 1931.
1219. MATSUDA, T. Über die Farbstoffausscheidung durch die Leber bei experimenteller Nierenstörung. *Jap. J. Gastroenterol.*, 6:315-48, 1934.
1220. MATSUO, I. Ausscheidung und Resorption der Farbstoffe. *Jap. J. Gastroenterol.*, 5:1-60, 1933.
1221. MATTHEWS, S. A. The effect of Eck's fistula on the formation of bile. *Proc. Am. Physiol. Soc.*, 29:27, 1911-12.
1222. MAURY, J. W. D. Is death in high intestinal obstruction due to the absorption of bile? *Ann. Surg.*, 46:556-67, 1907.
1223. MAXIMIN, M. Les Injections intraveineuses de sels biliaires en pathologie hépatique. Thèse. Paris, 1929.
1224. MAYER, C. Über die Gallenbildung bei Pflanzen. *Deutsche med. Wchnschr.*, 62:1922, 1936.
1225. MAYO, C., 2d, and GREENE, C. H. The role of the lymphatics in the early stages of the development of obstructive jaundice. *Am. J. Physiol.*, 89:280-88, 1929.
1226. MAYO, H. On the use of the bile. *London Med. and Physical J.*, Vol. 56 (N.S., Vol. 1), 340, 1826.
1227. MAYO, W. J., and MAYO, C. H. Surgery of the liver, the gallbladder and the biliary ducts. In *Keen's Surgery*, chap. li, pp. 966-1034, 1908.
1228. MAZZEO, M. Neutralizzazione della tossina dissenterica mediante la colesterina. *Rif. med.*, 44:1487-91, 1928.
1229. MCCLURE, C. W.; HUNTSINGER, M. E.; and FERNALD, A. T. The fatty acids of human duodenal bile, their quantitative separation estimation and the effect of foodstuffs on their secretion. *Am. J. Physiol.*, 107:1-12, 1934.

1230. McCLURE, C. W.; HUNTSINGER, M. E.; and FERNALD, A. T. Effects of administration of pure foodstuffs and inorganic substances on external secretory activities of the liver, pancreas and stomach. *Am. J. Physiol.*, **107**:94-112, 1934.
1231. McCLURE, C. W.; MENDENHALL, W. L.; and HUNTSINGER, M. E. The evaluation and treatment of disturbed liver function. *J.A.M.A.*, **85**:1537-40, 1935.
1232. McEACHERN, J. M., and GILMOUR, C. R. Studies in cholesterol metabolism. *Canad. M. A. J.*, **27**:153-57, 1932.
1233. McGOWAN, J. M. Bile salts in tolulenediamine jaundice. *Proc. Staff Meet. Mayo Clinic*, **10**:565-67, 1935.
1234. McGOWAN, J. M., BOLLMAN, J. L.; and MANN, F. C. The bile acids in icterus produced by tolulenediamine. *J. Pharmacol. & Exper. Therap.*, **58**:305-11, 1936.
1235. McGOWAN, J. M.; BUTSCH, W. L.; and WALTERS, W. Pressure in the common duct in man. *J.A.M.A.*, **106**:2227, 1936.
1236. McGUIRE, L. D. Drainage of the thoracic duct in peritonitis. *Surg. Gynec. Obst.*, **40**:626-30, 1925.
1237. McINDOE, A. H. Intrahepatic lithiasis associated with multiple internal biliary fistulas. *Surg. Clin. N. Am.*, **6**:1233-40, 1926.
1238. McMASTER, P. D. Do species lacking a gall bladder possess its functional equivalent? *J. Exper. Med.*, **35**:127-39, 1922.
1239. McMASTER, P. D. The influence of diet upon the output of cholesterol in the bile. *J. Exper. Med.*, **40**:25-42, 1924.
1240. McMASTER, P. D.; BROUN, G. O.; and ROUS, P. Studies on the total bile. *J. Exper. Med.*, **37**:395-420, 685-98, 1923.
1241. McMASTER, P. D., and ELMAN, R. Relation of the bile to the presence of urobilin in the body. *J. Exper. Med.*, **41**:513-34, 1925.
1242. McMASTER, P. D., and ELMAN, R. Absorption of pigments of biliary derivation from intestines. *J. Exper. Med.*, **41**:719-38, 1925.
1243. McMASTER, P. D., and ELMAN, R. Physiological variations in resistance to bile flow to intestines. *J. Exper. Med.*, **44**:151-71, 1926.
1244. McMASTER, P. D., and ELMAN, R. On the expulsion of bile by the gallbladder. *J. Exper. Med.*, **44**:173, 1926.
1245. McMASTER, P. D., and ROUS, P. Biliary obstruction required to produce jaundice. *J. Exper. Med.*, **33**:731-50, 1921.
1246. McNEE, J. W. Zur Frage des Cholestearingehalts der Galle während der Schwangerschaft. *Deutsche med. Wchnschr.*, **39**:994-97, 1913.
1247. McNEE, J. W. Experiments on haemolytic icterus. *J. Path. & Bact.*, **18**:325-42, 1913-14.
1248. McNEE, J. W. Cholesterin: an account of its relations to pathology and physiology. *Quart. J. Med.*, **7**:221-36, 1914.

1249. *McNEE, J. W. Jaundice: a review of recent work. *Quart. J. Med.*, 16:390-420, 1922-23.
1250. McROBERTS, J. W. The reaction of the duodenal content after exclusion of bile from the duodenum. *Am. J. Digest. Dis. & Nutrition*, 2:293-94, 1935.
1251. McVICAR, C. S. Diseases of the liver and biliary passages. *New York State J. Med.*, 27:109-13, 1927.
1252. McVICAR, C. S., and FITTS, W. T. Clinical aspects of jaundice. *J.A.M.A.*, 89:2018-21, 1927.
1253. McVICAR, C. S., and WEIR, J. F. Dissociated jaundice. *Med. Clin. N. Am.*, 10:499-508, 1926.
1254. MEDER, F. Über die Ausscheidung von Stoffen durch die Galle. Würzburg, 1892.
1255. MEIER, H. Die Beeinflussung der Harnabsonderung durch die Leber. *Biochem. Ztschr.*, 209:200-217, 1929.
1256. MEILLIÈRE, G. Recherche et caractérisation des acides biliaries dans l'urine. *Compt. rend. Soc. de biol.*, 74:844-47, 1913.
1257. MEISSNER, R. Über einfache und kombinierte Choleretika. *Arch. f. exper. Path. u. Pharmacol.*, 115:117-33, 1926.
1258. MELCHIOR, E. Zur Theorie der cholämischen Blutungen. *Beitr. z. klin. Chir.*, 139:162-69, 1927.
1259. MELCHIOR, E. Zur Kenntnis der perforationslosen Gallenperitonitis. *Deutsche Ztschr. f. Chir.*, 243:458-63, 1934.
1260. MELCHIOR, E.; ROSENTHAL, F.; and WISLICKI, L. Über das Krankheitsbild des Cholaskos. *Zentralbl. f. Chir.*, 54:194-96, 1927.
1261. MELCHIOR, E., and WISLICKI, L. Cholatintoxikation bei galliger Peritonitis. *Zentralbl. f. Chir.*, 54:1922-25, 1927.
1262. MELLANBY, J. Mechanism of pancreatic secretion. *Lancet*, 2:215-18, 1926.
1263. MELLANBY, J. Bile salts and secretin as cholagogues. *J. Physiol.*, 64:331-40, 1928.
1264. MELTZER, S. J., and SALANT, W. On the tetanic element in bile. *Proc. Soc. Exper. Biol. & Med.*, 2:54-55, 1904-5.
1265. MELTZER, S. J., and SALANT, W. The effects of intravenous injections of bile upon blood pressure. *J. Exper. Med.*, 7:280-91, 1905.
1266. MELTZER, S. J., and SALANT, W. The toxic effects of bile upon the central nervous system and the elimination of strychnine through the bile in nephrectomized animals. *J. Exper. Med.*, 8:127-66, 1906.
1267. MENDEL, L. B. Über das Vorkommen von Taurin in den Muskeln von Weichtieren. *Beitr. z. chem. Phys. u. Path.*, 5:582, 1904.
1268. MENTZER, S. H. Anomalous bile ducts in man. *J.A.M.A.*, 93:1273-78, 1929.

1269. MENTZER, S. H. Bile peritonitis. *Arch. Surg.*, **29**:227-41, 1934.
1270. MERTENS, V. E. Cholsäure Salz und Geschwulstwachstum. *Ztschr. f. Krebsforsch.*, **27**:295-307, 1928.
1271. MESTITZ, W., and RITTNER, S. Zur Bakteriologie der Galle und der Gallenblase. *Arch. f. klin. Chir.*, **153**:145-60, 1928.
1272. METZGER, E. Der Icterus neonatorum des Kalbes in vergleichender Hinsicht zu dem des Menschen. *Virchows Arch. f. path. Anat.*, **263**:703-18, 1927.
1273. METZGER, L. Menstrueller Ikterus. *München. med. Wchnschr.*, **52**:1145-46, 1905.
1274. MEULENGRACHT, E. [The clinical importance of the search for bile pigment in the serum.] *Ugesk. f. Læger.*, **81**:1785-99, 1919.
1275. MEULENGRACHT, E. Die klinische Bedeutung der Untersuchung auf Gallenfarbstoff im Blutserum. *Deutsches Arch. f. klin. Med.*, **132**:285-300, 1920.
1276. MEULENGRACHT, E. Ikterus Patogenese. *Ugesk. f. Læger.*, **50**:1103-6, 1925.
1277. MEYER, E. C., and HEINELT, H. Über den Einfluss des Gallefflusses und der Nahrungsaufnahme auf den Bilirubingehalt des Blutes und die Urobilinogenausscheidung mit dem Urin. *Deutsches Arch. f. klin. Med.*, **142**:94-109, 1923.
1278. MEYER, K. Über den Einfluss einiger Eiweiskörper und anderer Kolloide auf die Hämolyse. *Arch. f. Hyg.*, **65**:292-304, 1908.
1279. MEYER-BETZ, F. Untersuchen über die biologische (photodynamische) Wirkung des Hämatophorphyrins und anderer Derivate des Blut- und Gallenfarbstoffs. *Deutsches Arch. f. klin. Med.*, **112**:476-503, 1913.
1280. MEYERS, M. P., and ROSENBLATT, M. S. Bile in intestinal obstruction—experimental observations. *Surg. Gynec. Obst.*, **49**:473-76, 1929.
1281. MEYERSTEIN, W. Über die bakteriologische Bedeutung der Gallensalze. *Centralbl. f. Bakteriol.*, **44**:434-40, 1907.
1282. MEYTHALER, F., and JENNEMANN, K. Über die Schwankungen des Serumbilirubinspiegels bei Kurz-, Mittel- und Langstreckenläufen. *Med. Klin.*, **32**:1470-73, 1936.
1283. MEYTHALER, F., and PRIETSCHE, W. Anschauung über die Bedeutung von Leber und Galle im Altertum bis Galen. *Med. Welt.*, **10**:431-34, 1936.
1284. MICHAELIDÉS, N. A. Le Pouvoir antigénique de la bile dans la réaction de Wassermann. *Compt. rend. Soc. de biol.*, **97**:460-61, 1927.
1285. MICHAILOFF, M. P. [Influence of ligature of the ureters on secretion and composition of bile.] *Russian. St. Petersburg*, 1892.

1286. MICHEL, EVARISTE. De l'ictère hémaphéique. Thèse No. 229. Paris, 1868. Pp. 40.
1287. MIJERSON, A. J. Sympathicuswirling auf ein mit Galle durchströmtes Froschherz. Arch. néerl. de physiol., 21:567-73, 1936.
1288. MIKAMI, H. Über den Einfluss der Bakterien und der Ultraviolett- und Röntgenstrahlen auf Gallensäuren. J. Biochem., 14:489-500, 1932.
1289. MIKI, T. Glykogenbildung der Leber durch Gallensäure mit Adrenalin oder Insulin und das vegetative Nervensystem. Biochem. Ztschr., 247:445-58, 1932.
1290. MIKI, T. Die Glykogenbildung im Muskel durch Gallensäure bei Splanchnikotomie. Biochem. Ztschr., 247:459-64, 1932.
1291. MILLBOURN, E. On the diasturic conditions in cases of jaundice due to choledocholithiasis, acute hepatitis, and malignant tumors. Acta chir. Scandinav., 77:523-61, 1936.
1292. MILIO, G. Proprietà neutralizzante di alcuni componenti biliari sulla tossina difterica. Pediatria, 38:653-62, 1930.
1293. MILLS, M. A.; DRAGSTEDT, C. A.; and MEAD, F. B. Common bile duct obstruction and anaphylaxis. Proc. Soc. Exper. Biol. & Med., 34:469-70, 1936.
1294. MILNE, L. S. Congenital atresia of the bile passages. Quart. J. Med., 5:409, 1911-13.
1295. MILOVANOVIĆ, J. B., and STANOJEVIĆ, L. Über den Gallenfarbstoff im Blute beim dekompensierten Herz. Ztschr. f. klin. Med., 128:163-73, 1935.
- 1296.*MINKOWSKI, O. Die Störungen der Leberfunktion. Ergebn. d. allg. Pathol. u. path. Anat., 2:678-741, 1895.
1297. MINKOWSKI, O. Pathogenese des Ikterus. Ztschr. f. klin. Med., 55:34-43, 1904.
1298. MINKOWSKI, O., and NAUNYN, B. Beiträge zur Pathologie der Leber und des Icterus. Arch. f. exper. Path. u. Pharmakol., 21:1-33, 1886.
1299. MINNIBECK, H. Über die Gallensäuren in den Fäzes und deren Beziehung zur Fettresorption bei Kindern. Biochem. Ztschr., 257:160-70, 1933.
1300. MIRSKIY, I. [Hemolytic jaundice and biliary thrombi.] Russian. Russk. Klin., Moscow, 13:561, 1930.
1301. MISAKI, K. Bedeutung der Gallensäuren im Kohlenhydratstoffwechsel. J. Biochem., 8:235-59, 1928.
1302. MITANI, Y. Über den Einfluss der Leber-Diathermie auf die Gallensekretion. J. Biochem., 21:309-28, 1935.
1303. MITANI, Y. Über den Einfluss der Leber-Diathermie auf die Aus-

- scheidefähigkeit der Leber gegen körperfremde Farbstoffe. *J. Biochem.*, 21:381-97, 1935.
1304. MIZUNO, H. On the quantity of lactic acid in blood, bile, and urine during the disturbance of hepatic functions. *Jap. J. Gastroenterol.*, 3:175-91, 1931; 4:75-99, 1932.
1305. MOEBIUS, P. J. Über die Nieren beim Ikterus. *Arch. f. Heilk.*, 18: 83-100, 1877.
1306. MOLESCHOTT, J. Untersuchungen über die Bildungsstätte der Galle. *Arch. f. Heilk.*, 11:478-95, 1852.
1307. MOLFINO, F., and PATRONO, V. Ricerche sul comportamento della glicemia dopo somministrazione di alcuni derivati biliari. *Clin. med. ital.*, 67:493-500, 1936.
1308. MÖLLERSTRÖM, J. Periodicity of carbohydrate metabolism and rhythmic functioning of the liver. *Arch. Int. Med.*, 52:649-63, 1933.
1309. MONNERET, Ed. *Traité de pathologie générale*, 3:652, 1861.
1310. MONNERET, J. E. Etudes cliniques sur la maladie qui a reçu le nom de cirrhose du foie. Paris: Rignoux, 1852. Pp. 36. *Arch. gén. de méd.*, Paris, 1:641-77, 1852.
1311. MONNERET, J. E. A. De l'ictère hémorragique essentiel. Paris, 1859.
1312. MONTANARI, A. Ricerche sulla resistenza degli eritrociti nell'uomo di fronte alla bile e alla emolisina antiumana. *Riv. di clin. med.*, 31: 937-63, 1930.
1313. MOON, V. H., and MORGAN, D. R. Shock in bile peritonitis. *Proc. Soc. Exper. Biol. & Med.*, 34:743-47, 1936.
1314. MOOS, S. Untersuchungen und Beobachtungen über den Einfluss der Pfortaderentzündung auf die Bildung der Galle und des Zuckers in der Leber. *Habilitationsschrift zur Erlangung der "Venia docendi"* an der Universität Heidelberg. Leipzig u. Heidelberg: C. F. Winter, 1859. Pp. 30.
1315. MORAWITZ, P. Die Chemie der Blutgerinnung. *Ergebn. d. Physiol.*, 4:307-422, 1905.
1316. *MORAWITZ, P., and BIERICH, P. Über die Pathogenese der cholämischen Blutungen. *Arch. f. exper. Path. u. Pharmakol.*, 56:115-29, 1907.
1317. MORIGGIA, A. Di alcune proprietà della bile. Estratto dal T. 3, Serie 2 degli Atti d. R. Accad. d. Lincei, 2:95-113, 1876.
1318. MORISHIMA, T. [Physico-chemical studies on the blood in hepatic disturbance.] *Jap. J. Gastroenterol.*, 5:1776, 1930.
1319. MÖRNER, C. T. Cholic acid enterolithiasis. *Svenska läk-tidning*, 27: 659-60, 1930.
1320. MOSLER, F. Untersuchungen über den Übergang von Stoffen aus dem Blute in die Galle. *Diss. Giessen*, 1857.

1321. Moss, W. Experimental obstructive jaundice: its effect on fibrinogen and coagulation of the blood. *Arch. Surg.*, **26**:1-19, 1933.
1322. Mosse, M. Kommen der Galle fäulniswidrige und antibakterielle Eigenschaften zu? *Ztschr. f. klin. Med.*, **36**:527-34, 1898-99.
1323. MOYNIHAN, B. *Abdominal operations* (4th ed.), 2:528-29. Philadelphia and London: Saunders, 1926.
1324. MUIR, R., and HEGGIE, J. F. Haemoglobincolia in toxic conditions. *J. Path. & Bact.*, **40**:335-44, 1935.
1325. MÜLLER, A. Zur Frage des Einfluss des Lecithins auf die Löslichkeit der Ölsäure in Gallensäurelösungen. *Biochem. Ztschr.*, **249**:189-94, 1932.
1326. MÜLLER, E. Der Metallgehalt der Gallensteine und der Galle. *Biochem. Ztschr.*, **286**:182-85, 1936.
1327. MÜLLER, E. F. W. Über das Vorkommen von Aminosäuren und freiem Cholin in der Galle. *Ztschr. f. physiol. Chem.*, **242**:201-3, 1936.
1328. MÜLLER, F. Untersuchungen über den Icterus. *Ztschr. f. klin. Med.*, **12**:45-113, 1887.
1329. MÜLLER, G. P.; RAVDIN, I. S.; and RAVDIN, E. C. Alterations of bile pigment metabolism in biliary tract disease. *J.A.M.A.*, **85**:86-88, 1925.
1330. MÜLLER, H. Studien über die Bedeutung der Uringallensäuren für Klinik und Pathologie. *Schweiz. med. Wchnschr.*, **3**:110-17, 1922.
1331. MÜLLER, H. Über die Brauchbarkeit der Hay-Probe als Gallensäurenprobe im Urin. *Klin. Wchnschr.*, **3**:445-46, 1924.
1332. MÜLLER, J. *Elements of physiology*, p. 401. WILLIAM BALY (tr.). Philadelphia: Lea & Blanchard, 1843.
1333. MÜLLER, J. *Handbuch der Physiologie des Menschen für Vorlesungen*. 4 Aufl. Koblenz, 1844.
- 1334.*MÜLLER, KOLOMAN. Über Cholesterämie. *Arch. f. exper. Path. u. Pharmakol.*, **1**:213-48, 1873.
1335. MÜLLER, P., and ENGEL, L. Über das Absorptionsspektrum des Bilirubins in verschiedenen Lösungsmitteln. *Ztschr. f. physiol. Chem.*, **199**:117; **200**:145; **202**:56, 1932.
1336. MULLER, R. F. G. Über Pitta oder Galle, unter Bezug zur Tridosalehre der Altindischen Medizin. *Janus*, **38**:77-106, 1934.
- 1337.*MUNK, I. Galle. In *Real-Encyclopadie der gesamten Heilkunde*, **8**:197-209, 1895.
1338. MURAKAMI, K. Antagonistische Wirkung der Gallensäure gegen Adrenalin. *J. Biochem.*, **9**:261-70, 1928.
1339. MURAKAMI, K. Avitaminosen und Gallensäureausscheidung in der Galle. *J. Biochem.*, **9**:321-31, 1928.

1340. MURAO, S. Experimentelle Untersuchungen über das Auftreten der Rachitis. Das Auftreten der Rachitis bei Gallosterin als Lieferquelle des Vitamin A und normaler Proportion des Phosphor und Calciumgehalts der gebrauchten Salzmixtur. *J. Biochem.*, **23**:71-90, 1936.
1341. MURCHISON, CHARLES. A clinical lecture on diseases of the liver. 3d ed. London: Longmans, Green & Co., 1885. Pp. 544.
1342. MYLIUS, F. Über die blaue Iodstärke und die blaue Iodcholsäure. *Ztschr. f. physiol. Chem.*, **11**:306-47, 1887.
1343. MYLIUS, F. Zur Kenntnis der Pettenkofer'schen Gallensäurereaction. *Ztschr. f. physiol. Chem.*, **11**:492-96, 1887.
1344. NAKAGAWA, S., and FUJIKAWA, H. Eine neue quantitative Mikrobestimmungsmethode der Gallensäuren in der Galle. *J. Biochem.*, **12**:399-410, 1930.
1345. NAKAGAWA, S.; IMURO, S.; and SUZUKI, S. Gallensäurebelastungsprobe zur Leberfunktionsprüfung. *Klin. Wchnschr.*, **13**:1392-97, 1934.
1346. NAKAGAWA, S., and YOSHIKAWA, K. Über die Nakagawasche Extraktionsmethode für Gallensäuren aus der Galle und deren theoretische Überlegungen. *J. Biochem.*, **13**:321-41, 1931.
1347. NAKAJIMA, K., and KIMURA, K. Studies on the resistance of the erythrocytes in jaundice. *Jap. J. Gastroenterol.*, **2**:178, 1930.
1348. NAKATA, H. Über den Einfluss von Galle auf die Darmbewegungen. *Mitt. a. d. med. Akad. zu Kioto*, **7**:722-23, 1933.
1349. NASSE, H. Commentatio de bilis quotidie a cane secreta copia et indole. *Diss. Marburg*, 1851.
1350. NATHAN, M. Untersuchungen über den Cholesteringehalt von menschlichen Gallen. *Virchows Zrch. f. path. Anat.*, **228**:51-67, 1920.
1351. NATTAN-LARRIER, L., and GRIMARD-RICHARD, L. Perméabilité placentaire et glycocholate de soude. *Compt. rend. Soc. de biol.*, **112**:437-40, 1028-30, 1933.
1352. NATTAN-LARRIER, L.; GRIMARD-RICHARD, L.; and NOUGUÈS, S. Action de l'oléate de soude, des sels biliaires et de l'ovalbumine sur la perméabilité des ultra-filtres. *Compt. rend. Soc. de biol.*, **113**:540-42, 1933.
1353. NATTAN-LARRIER, L.; RICHARD, L.; and NOYER, B. Action de la bile sur la perméabilité placentaire. *Compt. rend. Soc. de biol.*, **104**:741-43, 1930.
1354. NAUMANN, H. N. Studies in bile pigment. A study of Ehrlich's test for urobilinogen and Schlesinger's reaction for urobilin. *Biochem. J.*, **30**:347-51, 1936.
1355. NAUNYN, B. Beiträge zur Lehre vom Icterus. *Arch. f. anat. Physiol. u. wissenschaft. Med.*, 1868, pp. 401-41.

1356. NAUNYN, B. Untersuchungen über Blutgerinnung in lebenden Thieren und ihre Folgen. Arch. f. exper. Path. u. Pharmakol., 1:1-17, 1873.
1357. NAUNYN, B. Klinik der Cholelithiasis. Leipsic, 1892.
1358. *NAUNYN, B. Über Ikterus und seine Beziehungen zu den Cholangien. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 31:537-600, 1918-19.
1359. NEDZVETSKII, S. W. (Nedswedski, S. W.). Fermentative Estersynthese des Cholesterins. Ztschr. f. physiol. Chem., 236:69-72, 1935.
1360. NEILSON, N., and MEYER, K. The reaction and physiology of the hepatic duct and cystic bile of various laboratory animals. J. Infect. Dis., 28:510-41, 1921.
1361. NEILSON, N., and MEYER, K. The bacteriostatic and germicidal properties of bile: experimental typhoid-paratyphoid carriers. J. Infect. Dis., 28:542-87, 1921.
1362. NELKEN, L. Zur Klinik und Pathogenese des Magen- und Duodenalgeschwürs. Arch. f. Verdauungskkrankh., 42:503-12, 1928.
1363. NEPPER, H. Recherches sur les substances anticoagulantes de la bile. Compt. rend. Soc. de biol., 60:362-64, 1906.
1364. NERON, P. Sur la bile, comme cause de maladies, et sur ses usages dans l'économie animale. Paris, 1803.
1365. NESTLE, L. Zur Frage des Ikterus beim Pferde. Tierarzt Leipzig, 51:17-26, 1912.
1366. NEUBAUER, E. Beiträge zur Kenntnis der Gallensekretion. Biochem. Ztschr., 109:82, 1920; 130:556, 1922; 146:480, 1924; 184:232, 1927.
1367. NEUBAUER, E. Dehydrocholsäure, einwirksames, praktisch ungiftiges Glied der Gallensäuregruppe. Klin. Wchnschr., 2:1065-67, 1923.
1368. NEUBAUER, E. Über die cholagoge Wirkung der Dehydrocholsäure beim Menschen. Klin. Wchnschr., 3:883, 1924.
1369. NEUBAUER, E. Über Verhalten und Wirkung von Gallensäuren im Organismus. Deutsche med. Wchnschr., 51:2150, 1925.
1370. NEUBAUER, E. Gallensekretion und Gallenentleerung. Wien. Arch. f. inn. Med., 18:365-72, 1929.
1371. NEUBAUER, E. Ist eine Konzentrationsänderung der Alkalien und Erdalkalien in der Lebergalle auf experimentellem Wege möglich? Arch. f. exper. Path. u. Pharmakol., 172:393-401, 1933.
1372. NEUFELD, F. Über eine spezifische bakteriolytische Wirkung der Galle. Ztschr. Hyg. u. Infektionskrankh., 34:454, 1900.
1373. NEUFELD, F., and ETINGER-TULCZYNSKA, R. Untersuchungen zur Gallenlösung der Pneumokokken. Arch. f. Hyg., 103:107-23, 1930.
1374. NEUFELD, F., and HÄNDEL. Beiträge zur Kenntnis der Wirkung verschiedener blutlösender Gifte, insbesondere des taurocholsäuren

- Natriums und der Seife. Arb. a. d. Kaiserl. Gesundheitsamte, 28: 572, 1908.
1375. NEUKOMM, J. Über die Nachweisung der Gallensäuren und die Umwandlung derselben in der Blutbahn. Vierteljahrsschrift der Naturforschenden Gesellschaft in Zürich, 5: 105-34, 1860.
1376. NEUKOMM, J. Über die Nachweisung der Gallensäuren und die Umwandlung derselben in der Blutbahn. Arch. f. Anat., Physiol., u. wissensch. Med., 1860, pp. 364-86.
1377. NEUKOMM, J. Über die Nachweisung der Gallensäuren und die Umwandlung derselben in der Blutbahn. Ann. d. Chem. u. Pharm., 116: 30-56, 1860.
1378. NEUMAN, F.; DEMOOR, P.; and DELOYERS, L. Contribution à l'étude de la pathogénie des ulcères gastroduodénaux: dérivation totale des sucs duodénaux biliaires et pancréatiques dans l'iléon terminal. Compt. rend. Soc. de biol., 105: 887-89, 1931.
1379. NEUMAN, F.; DEMOOR, P.; and DELOYERS, L. Contribution à l'étude de la pathogénie des ulcères gastroduodénaux: dérivation exclusive de la bile dans l'iléon terminal. Compt. rend. Soc. de biol., 105: 890-92, 1931.
1380. NEWMAN, C. E. Bilirubin and the van den Bergh reaction. Brit. J. Exper. Path., 9: 112-19, 1928.
1381. NEWMAN, C. E. Beiträge zum Studium des Gallenniederschlags und des Gallensteinbildung. Beitr. z. path. Anat. u. z. allg. Pathol., 86: 187-200, 1931.
1382. NICKEL, A. C., and JUDD, E. S. Cholecystitis: a bacteriologic and experimental study of three hundred surgically resected gallbladders. Surg. Gynec. Obst., 50: 655-62, 1930.
1383. NICOLLE, M. Séro-immunité vis-à-vis du "choléate de soude." Ann. de l'Inst. Pasteur, Paris, 21: 26-27, 1907.
1384. NICOLLE, M., and ADIL-BEY. Action de la bile sur le pneumocoque, et diverses autres bactéries. Ann. de l'Inst. Pasteur, Paris, 21: 20-25, 1907.
1385. NICOLOSI, G. Influenza della paratiroidi sul contenuto ematico di alcuni elettroliti nella derivazione completa della bile. Policlinico (sez. chir.), 40: 587-606, 1933.
1386. NIETHAMMER, E. Beiträge zur Kenntnis der Gallenfarbstoffe. Diss. Tübingen: Druck v. G. Schnürlein. 1907.
1387. NISIOKA, S. Über den Einfluss des Carotin und der Gallensäure auf die Glykogenie der Leber. Okayama-Igakkaï-Zasshi, 47: 2576, 1935.
1388. NISSEN, W. Experimentelle Untersuchungen über den Einfluss von Alkalien auf Secretion und Zusammensetzung der Galle. Dorpat, 1889.

1389. NOBEL, E. Über den Einfluss der Gallensäure auf die Herztätigkeit. *Ztschr. f. d. ges. exper. Med.*, 4:286-300, 1915.
1390. NONNENBRUCH, W. Über die Ausscheidung der Gallenfarbstoffe bei experimenteller Nephritis. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 31:470-72, 1918-19.
1391. NONNENBRUCH, W., and MAHLER, P. Chemische Untersuchungen pathologischer Lebergallen und deren Beeinflussung durch Karlsbader Mühlbrunn. *Med. Klin.*, 28:903-4, 1932.
1392. NORSI, G. Stati melanconici e bile nera. *Gazz. d. osp.*, 51:1201-3, 1930.
1393. NUCK, A. *Sialographia et ductuum aquosorum anatome nova . . . motus bilis circulari* (3d ed.), Part III, pp. 1-64. Lugd. Batavorum: Samuelem Luchtmans, 1723.
1394. NYGAARD, K. K. Coagulability of blood plasma. *Proc. Staff Meet. Mayo Clinic*, 7:544-47, 691-96, 1932.
1395. OBERMAYER, F. Knochenveränderungen bei chronischen Icterus. *Wien. klin. Rundschau*, 38:39, 1897.
1396. ODDI, R. Azione della bile sulla digestione gastrica, studiata col mezzo dello fistola colescisto-gastrica. *Arch. ital. d. biol.*, 9:138-42, 1888.
1397. OERTEL, H. Anatomic observations concerning the mechanism of bile resorption in jaundice. *Arch. Int. Med.*, 21:73-83, 1918.
- 1398.*OGATO, T. Beiträge zur experimentell erzeugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung der Gallenkapillaren bei der Unterbindung des Ductus choledochus unter der Ikterogenvergiftung. *Beitr. z. path. Anat. u. z. allg. Pathol.*, 55:236-321, 1912-13.
1399. OHASHI, K. Glykogenbildung der Leber bei Zufuhr von Hypophysenextrakt und Cholsäure. *J. Biochem.*, 20:59-63, 1934.
1400. OHASHI, K. Glykogenbildung der Leber und das pH des Harns von hungernden Kaninchen unter Einfluss von Gallensäure. *J. Biochem.*, 20:319-26, 1934.
1401. OHASHI, K. pH-Wert des Harns im Hunger und bei Stauungsikterus. *Arb. a. d. med. Fak. Okayama*, 4:583-88, 1935.
1402. OKA, T. Beitrag zum experimentellen mechanischen Icterus. Mikroskopischer Leberbefund des Hundes nach Choledochusunterbindung. *Klin. Wchnschr.*, 15:1170-71, 1936.
1403. OKADA, S. On the secretion of bile. *J. Physiol.*, 49:457-82, 1915.
1404. OKADA, S. Reaction of bile. *J. Physiol.*, 50:114, 1915.
1405. OKAMURA, S. Kreatininausscheidung bei experimentellen Stauungsikterus. *J. Biochem.*, 11:285-92, 1930.
1406. OKAMURA, S., and OKAMURA, T. Über die Gallensäure der Kanichengalle. *Ztschr. f. physiol. Chem.*, 188:11-16, 1930.

1407. OKAMURA, T. Über die Bufodesoxycholsäure in der Galle von *Bufo vulgaris japonica*. J. Biochem., 8:351-60, 1928; 10:5-9, 1928; 11:103-10, 1929.
1408. OKAMURA, T. Über den Einfluss der Gallensäuren auf die Nuclease-wirkung im Darm und in der Leber. J. Biochem., 8:391-96, 1928.
1409. OKAMURA, T. Bedeutung der Gallensäure im Kohlenhydratstoffwechsel. Zuckergehalt des Blutes. J. Biochem., 9:271-83, 1928.
1410. OKAMURA, T. Über den Einfluss des Gallensäureverlustes und der überschüssigen Gallensäurenzufuhr auf den Adrenalingehalt der Nebenniere. J. Biochem., 9:445-52, 1928.
1411. OKII, I. Die Calcium- und Phosphorsäurebilanz der Hündin bei Zufuhr von Gallensäure. J. Biochem., 18:45-61, 1933.
1412. OKII, I. Über den Einfluss der Gallensäure auf die Synthese der Phenolschwefelsäure im tierischen Organismus. J. Biochem., 20:31-35, 1934.
1413. OKII, I. Einfluss der Gallensäure auf die Glykogenbildung aus den Fettsäuren in der Leber. J. Biochem., 20:37-42, 1934.
1414. OKUIZUMI, C. Über die Giftigkeit des Harns. Jap. J. Med. Sc., 4:47-55, 1929.
1415. OLIVER, S. F. Studies on the bile and biliary diseases. Cincinnati J. Med., 4:186-96, 1923.
1416. OPIE, E. L. The etiology of acute hemorrhagic pancreatitis. Bull. Johns Hopkins Hosp., 12:182, 1901.
1417. OPIE, E. L. Diseases of the pancreas. 2d ed. Philadelphia: J. B. Lippincott Co., 1910.
1418. OPIE, E. L. Pathologic physiology of liver in relation to intoxication and infection. J.A.M.A., 85:1533-37, 1925.
1419. ORFILA, M. Nouvelles recherches sur l'urine des ictériques. Paris, 1821.
1420. ORLOFF, N. A. [On the peculiarities of the bile of children.] Russian. J. Russk. Obsh. Okhran. Narod. Zdrav., 8:530-41, 1898.
1421. ORNDORFF, W. R., and TEEPLE, J. E. On bilirubin, the red coloring matter of the bile. Am. Chem. J., 33:215-50, 1905.
1422. ORTH, O. Anikterische hämorrhagische Diathese bei Gallen fisteln. Chirurg, 7:144-47, 1935.
1423. OSHIMA, M. Clinical and experimental studies on urobilin-bodies. Jap. J. Gastroenterol., 3:67-70, 137-46, 1931; 4:41-51, 1932.
1424. OSLER, W., and MCCREA, T. Modern medicine, its theory and practice. 10th ed. New York: D. Appleton & Co., 1925.
1425. OSTERBERG, A. E. The new van den Bergh reaction for the determination of serum bilirubin utilizing the photometer. J. Lab. & Clin. Med., 22:729-35, 1937.

1426. OSTERHOUT, W. J. V. Decrease of permeability and antagonistic effects caused by bile salts. *J. Gen. Physiol.*, 1:405-8, 1919.
1427. OTT, I., and SCOTT, J. C. The action of animal extracts upon the flow of bile. *Proc. Soc. Exper. Biol. & Med.*, 13:12, 1915.
1428. OTT, I., and SCOTT, J. C. The action of bile and some of its constituents upon intestinal peristalsis and the circulation. *Proc. Soc. Exper. Biol. & Med.*, 5:13-18, 1908-9.
1429. OTTENBERG, R. Painless jaundice. *J.A.M.A.*, 104:1681-88, 1935.
1430. OTTENBERG, R., and KAHN, J. Relative immutability of hydrogen ion concentration of the bile: its buffering effect in bactericidal experiments. *Proc. Soc. Exper. Biol. & Med.*, 29:573-76, 1931.
1431. OZANAM, C. *La Circulation et le pouls, histoire, physiologie, séméiotique, indications thérapeutiques.* Paris, 1886.
1432. OYAMADA, S., and YAMAGUCHI, S. Accelerating action of bile in creating erythrocytes. *J. Orient. Med. (abst. sect.)*, 21:77, 1934.
1433. PAGÈS, HENRI. De la cholestérine et de son accumulation dans l'économie. Thèse Inaug. Strasbourg, 1869.
1434. PAGLIANI, F. Sul comportamento del calcio nelle ossa dopo derivazione totale della bile. *Ann. ital. di chir.*, 13:786-804, 1934.
1435. PAIJKULL, L. Über die Schleimsubstanz der Galle. *Ztschr. f. physiol. Chem.*, 12:196-210, 1888.
1436. PALMER, LE ROY S. Carotinoids and related pigments. New York: Chemical Catalog Co., Inc. (A.C.S.), 1922.
1437. PANCALOS, G. L'Action antitoxique de la bile sur les cultures de bacilles typhiques. *Compt. rend. Soc. de biol.*, 97:239-40, 1927.
1438. PANNETT, C. A., and WILSON, C. M. The influence of bile salts upon gastric function. *Brit. J. Exper. Pathol.*, 2:70-74, 1921.
1439. PAOLUCCI, F. Importanza della deviazione dei succhi pancreatico e biliare nella produzione delle ulcere gastriche e duodenali. *Ricerche sperimentali.* Morgagni, 73:883-94, 1931.
1440. PARACELSUS, THEOPHRASTUS. *Opera. De Icteritiis*, pp. 521, 556. Johannes Huser (ed.). *Brisgoium. Strassburg*, 1603. 1:486, *Genevae*, 1658.
1441. PARISOT, M. J. Etude sur les rapports de la rate, de l'ictère et de la fragilité globulaire. *Compt. rend. Soc. de biol.*, 12-2:91-96, 1911.
1442. PARKER, W. S. Metabolism of a child with complete absence of the bile from the intestines. *Am. J. Dis. Child.*, 5:386, 1913.
1443. PARSONS, L. G., and HICKMANS, E. M. Biliary cirrhosis. *Am. J. Dis. Child.*, 31:459, 1926.
1444. PASCHKIS, K. Über die Wirkung von choleretischen Mitteln, insbesondere des dehydrocholsäuren Natriums, auf die Galaktosetoleranz der Leber. *Klin. Wchnschr.*, 11:1418-20, 1932.

1445. PASCHKIS, H. Über Cholagoga. *Med. Jahrbücher*, pp. 159-72. Wien, 1884.
1446. PATEY, D. H. The experimental production of cholesterolosis (strawberry) gall-bladder. *Brit. J. Surg.*, 22:378-86, 1934.
1447. PATON, D. N. Observations on the composition and flow of the bile in man. *Brit. M. J.*, 1:960-61, 1892.
1448. PAUCHET, V. Bile noire et chirurgie. *Clinique, Paris*, 27:313-14, 1932.
1449. PAUCHET, V. Les Biles noires et la cholecystostomie. *Gaz. d. hôp.* 106:1629-31, 1933.
1450. PAVEL, I., and RADVAN, I. [Experimental studies on biliary secretions.] *Spitalul*, 50:52-55, 1930.
1451. PAVLOV, I. P. [Osteoporosis caused by exclusion of bile from intestinal tract.] *Russian. Verhandl. Ges. russ. Aertz.*, 72:314, 1904.
1452. PECCO, R. Su le ulcere gastroduodenali che compaiono in seguito alla derivazione della bile. Osservazioni sperimentali. *Arch. ital. di chir.*, 30:23-44, 1931.
1453. PENNETTI, G. La Bilirubinemia da raggi ultravioletti. *Arch. di radiol., Napoli*, 1:51-59, 1925.
1454. PENNETTI, G. La Composizione della bile nelle varie alimentazioni. *Riforma med.*, 46:1701-4, 1930.
1455. PEOPLES, S. A. A simplified method for determining bile salts in bile. *Proc. Soc. Exper. Biol. & Med.*, 30:1117-20, 1933.
1456. PERICHANJANZ, J. I. [On the effect of bile constituents on nerves.] *Russian. Wratschebnoje delo*, No. 22-24, 1921.
1457. PERICHANJANZ, J. I. Über die Wirkung von Gallensubstanzen auf die Nerven. *Chem. Zentralbl.*, 3:637, 1922.
1458. PERLZWEIG, W. A., and BARRON, E. C. New colorimetric method for determination of bile acids in blood. *Proc. Soc. Exper. Biol. & Med.*, 24:233-34, 1926.
1459. PESCH, K. L., and HOFFMANN, V. Nochmals zur Bakteriologie der Gallenwege. *München. med. Wchnschr.*, 77:365, 1930.
1460. PETOW, H., and WITTKOWER, E. Studien über die Acidität der Zellen und Gewebe. Beiträge zur Vitalfärbung mit Indicatorfarbstoffen. *Ztschr. f. d. ges. exper. Med.*, 64:736-56, 1929.
1461. PETRÉN, G. Über die postoperativen letal verlaufenden sog. cholämischen Blutungen. *Beitr. z. klin. Chir.*, 110:237-329, 1917.
1462. PETRÉN, G. Untersuchungen über die Blutgerinnung bei Icterus. *Beitr. z. klin. Chir.*, 120:501-88, 1920.
1463. PETRÉN, G. Untersuchungen über die Blutgerinnung bei Ikterus nebst einigen Worten über die sog. cholämischen Blutungen. *Acta chir. Scandinav.*, 58:488-522, 1925.

1464. PETROFF, J. R. Zur Analyse der Gallentreibenden Wirkung der intravenös injizierten Galle. *Ztschr. f. d. ges. exper. Med.*, 45:424-27, 1925.
1465. PETTENKOFER, M. J. Notiz über eine neue Reaction auf Galle und Zucker. *Ann. Chem. u. Pharm.*, 52:90, 1844.
1466. PEYRI, J. J. E. Contribution à l'étude de l'action nervolytique de la bile et des sels biliaires. Bordeaux, 1906.
1467. PEZCOLLER, A. Contributo allo studio del coleperitoneo sperimentale. *Arch. ital. di chir.*, 33:677-706, 1933.
1468. PFAFF, F., and BALCH, A. W. An experimental investigation of some of the conditions influencing the secretion and composition of human bile. *J. Exper. Med.*, 2:49-105, 1897.
1469. PFANNENSTIEL, W., and KORTMANN, T. Die Verwendung Gallensäurer Salze zum Nachweis. Pathogener Darmbakterien im Blute. München. med. Wchnschr., 75:1241-43, 1928.
1470. PFANNENSTIEL, W., and KORTMANN, T. Nachweis pathogener Darmkeime im Blute mittels taurocholsäuren Natriums. München. med. Wchnschr., 76:408-9, 1929.
1471. PFLÜGER, E. Die "postmortale" Secretion der Galle. *Arch. f. d. ges. Physiol.*, 4:54-56, 1871.
1472. PFUGHÖFT, L. Experimentelles über die Pathogenese der Cholaemie. Diss. Göttingen, 1904.
1473. PHILLIPS, J. Congenital obliteration of bile ducts. *Oxford Monographs on Diagnosis and Treatment*, 8:390-98, 1930.
1474. PICK, E. Zur Kenntniss der Leberveränderungen nach Unterbindung des Ductus choledochus. *Ztschr. f. Heilk.*, 11:117-28, 1890.
1475. PIERCE, R. M.; AUSTIN, J. H.; and EISENBREY, A. B. The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. *J. Exper. Med.*, 16:375-94, 1912.
1476. PILZECKER, A. Gallenuntersuchungen nach Phosphor- und Arsenvergiftung. *Ztschr. f. physiol. Chem.*, 41:157-76, 1904.
1477. PINCOFFS, M. C., and BOGGS, T. R. Diseases of peritoneum. *Oxford Med.*, 3:Part II, chap. ix, 539, 1920—.
1478. PIORRY, P. A., and LHÉRITIER, D. Cholihémie, ictère, jaunisse, morbus regius. Paris, 1840.
1479. PISENTI, G. Sulle modificazioni della secrezione biliare nei processi febbrili. *Arch. per le sc. med.*, 9:10, 1885.
1480. PISENTI, G. Über die Veränderungen der Gallenabsonderung während des Fiebers. *Arch. f. exper. Path. u. Pharmacol.*, 21:219-48, 1886.
1481. PLAESTERER, R. Über die giftigen Wirkungen des Bilirubins. Inaug. Diss. Würzburg: Laboratorium v. Kunkel, 1890. Pp. 22.

1482. PLATNER, E. A. Mittheilungen über die Galle. Arch. f. Anat., Physiol. u. wissensch. Med., 1844, p. 94. Ann. d. Chem., 51:105-11, 1844.
1483. PLATNER, E. A. Über die Natur und den Nutzen der Galle. Heidelberg: Julius Groos, 1845. Pp. 129.
1484. PLATNER, E. A. Über die Darstellung und die Bestandtheile der in der Galle enthaltenen krystallisirbaren Natronverbindung. J. f. prakt. Chem., Leipzig, 11:129-33, 1847.
1485. *PLATNER, E. A. Die Galle. 1847.
1486. PLINII, C., Secundi. Naturalis Historiae cum selectis doctorum Virarum Commentariis. Lugd. Batav et Roterodami. Apud Hackios (ex officina Hakiana), 1669.
1487. POHL, J. Physiologische Wirkungen neuer Gallensäuren. Ztschr. f. d. ges. exper. Med., 30:423-31, 1922.
1488. POLIMANTI, O. La Tossicità della bile del bue e del vitello. Bollettino della R. Accad. med. di Roma, 21:1894-95. Inst. di farmacol. sper., 3:193-228, 1896.
1489. POLIMANTI, O. Die Toxicität der Ochsen und Kalbsgalle. Moleschotts Untersuchungen, 16:131-69, 1899.
1490. PONCET, A. De l'ictère hématique traumatique. Thèse. Paris, 1874.
1491. PONDER, E. The relation between bile salts and haemolysis in the blood stream. Brit. J. Exper. Path., 2:289-91, 1921.
1492. PONDER, E. A method for examining the haemolytic activity of chemical substances. Proc. Roy. Soc. Med., 92:285-95, 1921.
1493. PONDER, E. Animal experiments in the inhibition of haemolysis by blood serum. Quart. J. Exper. Physiol., 13:283, 1923; 14:25-35, 1924.
1494. PONDER, E., and GORDON, A. S. The kinetics of haemolysis in cell-taurocholate-serum systems. Proc. Roy. Soc. London, s. B., 117:272-88, 1935.
1495. PONDER, E., and YEAGER, J. F. The inhibitory effect of sugars on haemolysis by sodium taurocholate. Biochem. J., 22:703-10, 1928.
1496. POPP, O. Harnstoff als normaler und constanter Bestandtheil der Galle. Ann. d. Chem., 156:88-90, 1870.
1497. POPPER, H. L. Pankreasfermente in der Galle. Zentralbl. f. Chir., 40:2515-17, 1929.
1498. POPPER, H. L. Pankreassaft in den Gallenwegen. Arch. f. klin. Chir., 175:660-95, 1933.
1499. POPPER, H., and GERZNER, L. Über den Bakterienübertritt in die Galle. Ztschr. f. klin. Med., 128:547-59, 1935.
1500. POPPER, L. Über die Einwirkung von Bilirubinzufuhr auf das Blut. Klin. Wchnschr., 9:1770, 1930.

1501. PORTAL, A. Observation sur la nature et le traitement des mals du foie. Paris: Longchamps, 1813. Pp. 646.
1502. PORTER, L. Diseases of the liver. In ABT, Pediatrics, 3:634-77. Philadelphia: W. B. Saunders Co., 1924.
1503. POTTER, J. C., and MANN, F. C. Pressure changes in the biliary tract. Am. J. Med. Sc., 171:202-17, 1926.
1504. POTTER, M. G. Observations of the gallbladder and bile during pregnancy at term. J.A.M.A., 106:1070-74, 1936.
1505. POUZOL, T. Essai sur l'ictère, No. 167. Paris, 1872. Pp. 124.
1506. POWELL, R. Observations on the bile and its diseases. London: F. & C. Rivington, 1800. Pp. 180.
1507. POWER, S. Biliary peritonitis. Brit. M. J., 2:948-49, 1935.
1508. POZZI, G. Sulla "causa mortis" nella peritonite biliare. Arch. ed atti d. Soc. ital. di chir., 39:816-22, 1933.
1509. PRÈVOST, M., and BINET, L. Recherches expérimentales relatives à l'action des médicaments sur la sécrétion biliaire et à leurs élimination par cette sécrétion. Compt. rend. Soc. de biol., 106:1690-94, 1888. Rev. méd. de la Suisse Rom., 8:249, 1888.
1510. PRIBRAM, B. O. Die hepatitischen Residualbeschwerden nach Galenoperationen. Deutsche med. Wchnschr., 55:1768, 1801, 1929.
1511. PRICE, I. N. O. Some observations on the action of certain sodium bile salts on the gonococcus. Brit. J. Ven Dis., 9:50-54, 1933.
1512. PRITZKER, B. Experimentelle Prüfung der toxischen Wirkung von Galle und Gallenbestandteilen bei subduraler Applikation; zugleich ein Beitrag zur Toxikologie des subduralen Hämatoms. Deutsche Ztschr. f. Chir., 243:85-95, 1934.
1513. PRÖSCHER, H. Über Acetophenonazobilirubin. Ztschr. f. physiol. Chem., 2:411, 1900.
1514. PROUT, W. Chemistry, meteorology, and the function of digestion considered with reference to natural theology. Bridgewater treatise. London, 1834.
1515. PRUSZYŃSKI, J. [Composition of human bile.] Polish. Gaz. lek. Warszawa, 26:227-32, 1906.
1516. PUCHER, G. W., and SLY, G. E. A comparative chemical analysis of fistula bile and gallbladder bile for sugar and non-protein nitrogen fractions. Buffalo Gen. Hosp. Bull., 6:3-13, 1928.
1517. PUESTOW, C. B. The discharge of bile into the duodenum. An experimental study. Arch. Surg., 23:1013-29, 1931.
1518. PUGLIESE, A. Nouvelles recherches sur la sécrétion et sur la composition de la bile chez les animaux privés de la rate. Arch. ital. biol., Torino, 38:257-72, 1902.
1519. QUAGLIARIELLO, G. Sulla reazione chimica della bile. Rend. R. Accad. d. Lincei, 20:302, 1911.

1520. QUEEN, F. B.; HAWKINS, W. B.; and WHIPPLE, G. H. Splenectomy in bile fistula dogs: bile pigment overproduction, anemia and intoxication. *J. Exper. Med.*, **57**:399-418, 1933.
1521. QUÉNU, E.; DUVAL, P.; and BRULÉ, M. Etudes sur la cholémie, post-anesthésique et sur les moyens de la modifier. *Bull. et mém. Soc. de chir. de Paris*, **45**:833, 1919.
1522. QUESNAY, M. *Essai physique sur l'oeconomie animale* (2d ed.), 3. Paris, 1747.
1523. QUICK, A. J. The coagulation defect in sweet clover disease and in the hemorrhagic chick disease of dietary origin: a consideration of the source of prothrombin. *Am. J. Physiol.*, **118**:260-71, 1937.
1524. QUICK, A. J.; STANLEY-BROWN, M.; and BANCROFT, F. W. A study of the coagulation defect in hemophilia and in jaundice. *Am. J. M. Sc.*, **190**:501-11, 1935.
1525. QUINCKE, H. Beiträge zur Lehre vom Icterus. *Virchows Arch. f. path. Anat.*, **95**:125, 1884.
1526. QUINCKE, H., and HOPPE-SEYLER, G. Die Krankheiten der Leber. *Nothnagels Handbuch*, 1889, p. 72.
1527. QUINCKE, H., and HOPPE-SEYLER, G. Die Krankheiten der Leber. In C. W. H. NOTHNAGEL, *Specielle Pathologie und Therapie*, **184**:1-680. Wien: A. Hölder, 1899.
1528. QUINCKE, H., and HOPPE-SEYLER, G. Diseases of the liver. In R. H. FITZ, *Diseases of the liver, pancreas and suprarenal capsules*, pp. 383-904. Philadelphia: W. B. Saunders & Co., 1905.
1529. RABBONI, F. Alterazioni anatomiche del cuore e grossi vasi dopo derivazione totale della bile associata o no ad emiparatiroidectomia. *Pathologica*, **26**:120-28, 1934.
1530. RABBONI, F. La Alterazioni funzionali del fegato nella derivazione totale della bile dall'intestino. *Arch. di biol.*, **88**:203-17, 1934.
1531. RABINOWICH, I. M. The renal threshold of bilirubin. *J. Biol. Chem.*, **97**:163-75, 1932.
- 1532.*RABL, C. R. H. Experimentelle Untersuchungen über Osteoporose und Rachitis. *Arch. f. klin. Chir.*, **137**:619-34, 1925.
1533. RABL, R. Untersuchungen zur Morphologie der Gallensekretion. *Jahresb. f. morph. u. micro. Anat.*, **2**. Abt, **23**:71-97, 1930.
1534. RACHFORD, B. K. The influence of bile on the fat-splitting properties of pancreatic juice. *J. Physiol.*, **12**:72-94, 1891.
1535. RAHMLOW, H., and RITTERBAND, H. Zur Dehydrocholsäure Diurese. *Deutsche med. Wchnschr.*, **52**:1992, 1926.
1536. RANC, A. Extraction de la bilirubine du plasma du sang de cheval. *Compt. rend. Soc. de biol.*, **62**:306-7, 1907.
1537. RANC, A. Sur la matière colorante du plasma du sang de cheval. *Compt. rend. Soc. de biol.*, **62**:496-97, 1907.

1538. RANKE, J. Untersuchung über die chemischen Bedingungen der Ermüdung des Muskels. *Arch. f. Anat., Physiol. u. wissensch. Med., Physiol. Abt.*, 1864, pp. 340-43. Tetanus, Leipzig, 1865, p. 395.
1539. RANKE, J. Die Blutvertheilung und Thätigkeitswechsel der Organe, pp. 9 and 173. Leipzig, 1871.
1540. RAUE, F. Über den Gallensäurestoffwechsel. Eine neue Methode zur quantitativen Schätzung der Gallensäures. *Ztschr. f. klin. Med.*, 102:79-85, 1926.
1541. RAVDIN, I.; JOHNSTON, C.; AUSTIN, J.; and RIEGEL, C. The absorption of chloride from the bile-free gall bladder. *Am. J. Physiol.*, 99: 638-47, 1932.
1542. RAVDIN, I. S.; JOHNSTON, C. G.; RIEGEL, C.; and WRIGHT, S. L. A study of human liver bile after release of common duct obstruction. *J. Clin. Investigation*, 12:659-72, 1933.
1543. RAVDIN, I. S.; MORRISON, M. E.; and SMYTH, C. M. Bile peritonitis and bile ascites. *Ann. Surg.*, 89:867-77, 1929.
1544. RAVDIN, I. S.; RIEGEL, C.; and MORRISON, J. L. Coagulation of blood. *Ann. Surg.*, 91:801-10, 1930.
1545. RAVDIN, I. S.; RIEGEL, C.; and MORRISON, P. J. The haemorrhagic tendency in obstructive jaundice. *Ann. Surg.*, 101:605-12, 1935.
1546. RAWLS, W.; WEISS, S.; and COLLINS, V. Liver function in rheumatoid (chronic infectious) arthritis; preliminary report. *Ann. Int. Med.*, 10:1021-27, 1937.
1547. REDI, R. La Permeabilità intestinale e la alterazioni anatomopatologiche dell'intestino, in animali portatori di fistola biliare con derivazione completa della bile all'esterno. *Atti d. R. accad. d. fisiocrit. in Siena*, 5:210-19, 1930.
1548. REGAN, J. F., and HORRALL, O. H. The physiologic action of dehydrocholic acid. *Am. J. Physiol.*, 101:268-73, 1932.
1549. REIMANN, H. A. Variations in specificity and virulence of pneumococci during growth in vitro. *J. Exper. Med.*, 5:587, 1925.
1550. REINBACH, G. Über den Einfluss der vernösen Stauung auf die Secretion der Galle. Breslau, 1894.
1551. REINHOLD, J. G., and WILSON, D. W. The acid-base composition of hepatic bile. *Am. J. Physiol.*, 107:378-87, 1934.
1552. REINHOLD, J. G., and WILSON, D. W. The acid-base composition of hepatic bile: the changes induced by the injection of hydrochloric acid and inorganic salts. *Am. J. Physiol.*, 107:388-99, 1934.
1553. REINHOLD, J. G., and WILSON, D. W. The acid-base composition of hepatic bile. The effects of the administration of sodium taurocholate, sodium cholate and sodium dehydrocholate. *Am. J. Physiol.*, 107:400-405, 1934.

1554. RENAUD, C. H. Essai sur la physiologie du foie. Thèse. Strasbourg, 1836. Pp. 31.
1555. RENAULDIN, M. Bile. Dictionnaire des sciences médicales, 3: 125-38, 1818.
1556. RETZLAFF, O. Über Gallenergüsse in das Bauchfell und deren Spätfolgen. Arch. f. klin. Chir., 153: 745-49, 1928.
1557. REWBRIDGE, A. G. Etiological role of gas bacilli in bile peritonitis. Proc. Soc. Exper. Biol. & Med., 27: 528, 1930.
1558. REWBRIDGE, A. G. Etiological role of gas-forming bacilli in experimental bile peritonitis. Surg. Gynec. Obst., 52: 205-11, 1931.
1559. RIBIERRE, P. L'Hémolyse et la mesure de la résistance globulaire; application à l'étude de la résistance globulaire dans l'ictère. Paris, 1903.
1560. RICCIUTI, G. Bradicardia in ferite e lesione contusive del fegato. Policlinico (sez. chir.), 34: 229, 1927.
1561. RICH, A. R. The formation of bile pigment from haemoglobin in tissue cultures. Bull. Johns Hopkins Hosp., 25: 415, 1924.
1562. RICH, A. R. The formation of bile pigment. Physiol. Rev., 5: 182-224, 1925.
1563. RICH, A. R. Pathogenesis of the forms of jaundice. Bull. Johns Hopkins Hosp., 47: 338-77, 1930.
1564. RICH, A. R., and BLUMSTEAD, J. H. On the identity of hemaetoidin and bilirubin. Bull. Johns Hopkins Hosp., 36: 225-32, 1925.
1565. RICH, A. R., and BLUMSTEAD, J. H. Alleged power of bacteria to form bile pigment from hemoglobin. Bull. Johns Hopkins Hosp., 36: 376, 1925.
1566. RICH, A. R., and REINHOFF, W. F., JR. The bile-pigment content of the splenic vein. Bull. Johns Hopkins Hosp., 36: 431-36, 1925.
1567. RICHARDS, E. T. F., and JOHNSON, W. C. Study of a case of congenital hemolytic jaundice. J.A.M.A., 61: 1586-91, 1913.
1568. RICHARDSON, M. L. Biliary cirrhosis in the rabbit. J. Exper. Med., 14: 401-7, 1911.
1569. RICHET, C. Dictionnaire de physiologie, 2: 144-209. Paris: Alcon, 1897.
1570. RIEGEL, F. Über Verlangsamung der Schlagfolge des Herzens. Ztschr. f. klin. Med., 17: 252, 1890.
1571. RIEGEL, C.; ELSOM, K. O.; and RAVDIN, I. S. The influence of sodium taurocholate, hepatic bile and gall-bladder upon the absorption of oleic acid from the small intestine. Am. J. Physiol., 112: 669-72, 1935.
1572. RIEGEL, C.; RAVDIN, I. S.; and JOHNSTON, C. The absorption of bile salts and cholesterol from the bile-free gall bladder. Am. J. Physiol., 99: 656-65, 1932.

1573. RIEGEL, C.; RAVDIN, I. S.; JOHNSTON, C. G.; and MORRISON, P. J. The composition of gall-bladder bile and calculi in gall-bladder disease. *Surg. Gynec. Obst.*, 62:933-40, 1936.
1574. RIEGEL, C.; RAVDIN, I. S.; MORRISON, P. J.; and POTTER, M. J. The composition of gallbladder bile in pregnancy. *J.A.M.A.*, 105: 1343-44, 1935.
1575. RIES, F., and STILL, E. U. Toxicity of purified bile preparations: influence on cardiovascular responses. *Arch. Int. Med.*, 51:90-99, 1933.
1576. RIES, F. A., and STILL, E. U. On the toxicity of purified bile preparations. *Am. J. Physiol.*, 91:607-17, 1930.
1577. RIESMAN, D. Pre-icteric itching. *Ann. Med.*, 13:77-79, 1907.
1578. RIGOBELLO, G. Comportement des sels et des acides biliaires dans la lysis du pneumocoque. *Soc. internaz. di microbiol., Boll. d. sez. ital.*, 2:330-32, 1930.
1579. RISI, A. Sull'azione farmacodinamica della bile. Tossicologia, circolazione, respirazione, cuore isolato e ricerche emato-refrattometriche. *Arch. internat. de pharmacodyn. et de thérap.*, 52:17-32, 1935.
1580. RITTER, J. F. Einige Versuche über die Abhängigkeit d. Absondnungs-grosse der Galle von der Nahrung. *Inaug. Diss. Marburg*, 1862.
1581. RITTER, M. E. Quelques observations de bile incolore. *J. de l'anat. et de la physiol.*, 1872, pp. 181-86.
1582. RITTERBAND, H. Beitrag zur Wirkung der Gallensäuren. *Inaug. Diss. Berlin*, 1926.
1583. ROBERTSON, W. E.; SWALM, W. A.; and KONZELMANN, F. W. Functional capacity of the liver. *J.A.M.A.*, 99:2071-78, 1932.
1584. ROBIN, C. P. Leçons sur les humeurs normales et morbides du corps de l'homme. Paris: J. B. Baillière & fils, 1867.
1585. ROBSON, A. W. MAYO. Observations on the secretion of bile in a case of biliary fistula. *Proc. Roy. Soc. Med.*, 47:499-524, 1890.
1586. ROBSON, A. W. MAYO. Pancreatic catarrh and interstitial pancreatitis in their relation to catarrhal jaundice and also to glycosuria. *Surg. Gynec. Obst.*, 6:29-39, 1908.
1587. ROBUSCHI, L., and CONSTANTINI, A. L'Action du taurocholate de soude sur la perméabilité du placenta et sur l'anaphylaxie héréditaire. *Soc. internaz. di microbiol., Boll. d. sez. ital.*, 7:11-17, 1935.
1588. ROCCAVILLA, A. L'Action locale de la bile et du serum cholémique sur le cœur et les vaisseaux sanguins isolés des mammifères. *Arch. d. méd. expér. et d'anat. path.*, 25:552-80, 1913.
1589. ROGER, G. H. Action du foie sur les poisons. Paris, 1887.

1590. ROGER, G. H. Rôle du foie dans les auto-intoxications. *Gaz. d. hôp.*, 66:525, 1887.
1591. ROGER, G. H. *Physiologie normale et pathologique du foie*. Paris, 1922.
- 1592.*ROGER, G. H. *Physiologie du foie*. In *Traité de physiologie normale et pathologique*, 3:1-252. Paris: Masson et Cie, Editeurs, 1928.
1593. ROGER, G. H.; WIDAL, F.; and TEISSIER, P. F. *Pathologie du foie*. *Nouveau traité de médecine*, 16:1048, 1928.
1594. ROGER, H. Les intoxications. In C. BOUCHARD, *Traité de pathologie générale*, 1:780, 1895.
1595. ROGER, H. Influence de la bile sur la putréfaction des matières azotées. *Compt. rend. Soc. de biol.*, 73:274-76, 1912.
1596. ROGER, H. Quelques considérations sur le rôle de la bile. *Presse méd.*, 21:No. 15, 137-39, 1913.
1597. ROGER, H. Influence de la bile sur les putréfactions intestinales. *Arch. des maladies de l'app. digestif*, Mai, 1913.
1598. ROGER, H. Le Rôle antiputride de la bile. *Ann. de l'Inst. Pasteur*, 29:545-50, 1915.
1599. ROGER, H. Sur les ferments. *Presse méd.*, 27:741-42, 1919.
1600. ROGERS, H. La Coagulation de la mucine. *Compt. rend. Soc. de biol.*, 59:423, 1905.
1601. ROGERS, H. Digestion et nutrition, 1:565-68, Paris, 1910.
1602. RÖHMANN, F. Beobachtung an Hunden mit Gallenfistel. *Habilitationsschrift*. Breslau, 1882. *Pflügers Arch.*, 29:509, 1882.
1603. RÖHRIG, A. Über den Einfluss der Galle auf die Herzthätigkeit. *Inaug. Diss.* Leipzig, 1863.
1604. RÖHRIG, A. Über den Einfluss der Galle auf die Herzthätigkeit. *Arch. d. Heilk.*, 4:385-419, 1863.
1605. RÖHRIG, A. Experimentelle Untersuchungen über die Physiologie der Gallenabsonderung. *Medizinische Jahrbücher*, Wien, 1:243-73, 1873.
1606. ROLLESTON, SIR H. D. Jaundice. In BALLANTYNE, *Encyclopaedia Medica* (2d ed.), 7:130-58. Edinburgh: W. Green & Son, 1921.
1607. ROLLESTON, H., and McNEE, J. W. *Diseases of the liver, gallbladder, and bile ducts*. 3d ed. London: Macmillan & Co., 1929.
1608. ROMEO, M. Sulle alterazioni dei reni nella colemia sperimentale. *Ann. ital. chir.*, 8:1376-1402, 1929.
1609. ROSENAK, B. D., and KOHLSTAEDT, K. G. Bile salt therapy in liver and gall bladder disease. *Am. J. Digest Dis. & Nutrition*, 3:577-80, 1936.
1610. ROSENBERG, E. The etiology and treatment of gastric and duodenal ulcer. (The use of cholesterin and bile salts.) *Clin. Med. & Surg.*, 35:168-71, 1928.

1611. ROSENBERG, L., and JUDD, G. E. Congenital atresia of the bile ducts. *Arch. Surg.*, 18:233-39, 1929.
1612. ROSENBLOOM, J. A quantitative chemical analysis of human bile. *J. Biol. Chem.*, 14:241-43, 1913.
1613. ROSENOW, E. C. The etiology of cholecystitis and gall-stones and their production by intravenous injection of bacteria. *J. Infect. Dis.*, 19:527-56, 1916.
1614. ROSENTHAL, F. Die Galle. *Handbuch der normalen und pathologischen Physiologie*, 3:876-909, 1927.
1615. ROSENTHAL, F. Über das Wesen und die Behandlung des Hautjuckens beim Ikterus. *Therap. d. Gegenw.*, 70:297-301, 1929.
1616. ROSENTHAL, F. Das Problem der Bildungsstätten des Gallenfarbstoffes. *Klin. Wchnschr.*, 11:441-46, 1932.
1617. ROSENTHAL, F., and FALKENHAUSEN, M. F. von. Über eine quantitative Bestimmung der Glykocholsäure und Taurocholsäure in der menschlichen Duodenalgalle. *Klin. Wchnschr.*, 2:1111, 1923.
1618. ROSENTHAL, F., and FALKENHAUSEN, M. F. von. Beiträge zur Physiologie und Pathologie der Gallensekretion. *Arch. f. exper. Path. u. Pharmakol.*, 98:321, 1923.
1619. ROSENTHAL, F.; FALKENHAUSEN, M. F. von; and FREUND, H. Über das Phänomen des Umkehr der Gallensäurenrelationen in der Galle von Leberkranken. *Arch. f. exper. Path. u. Pharmakol.*, 111:170-81, 1925-26.
1620. ROSENTHAL, F., and LAUTERBACH, F. Beiträge zur Physiologie und Pathologie der Gallensekretion. *Arch. f. exper. Path. u. Pharmakol.*, 101:1, 1924.
1621. ROSENTHAL, F., and WISLICKI, L. Über eine quantitative Bestimmung der Gallensäuren im Blut. *Arch. f. exper. Path. u. Pharmakol.*, 117:8-23, 1926.
1622. ROSENTHAL, F., and WISLICKI, L. Gallensäuren-Studien am ikterischen Menschen. *Klin. Wchnschr.*, 6:781-84, 1927.
1623. ROSENTHAL, F.; WISLICKI, L.; and POMMERELLE, H. Der Abbau der Gallensäuren im Organismus. *Arch. f. exper. Path. u. Pharmakol.*, 122:159-83, 1927.
1624. ROSENTHAL, F., and ZINNER, K. Über den Gallensäuregehalt der A- und B-Galle zugleich ein Beitrag über die Konzentrations- und Resorptionsleistungen der Gallenblase. *Ztschr. f. d. ges. exper. Med.*, 78:498-510, 1931.
1625. ROSENTHAL, N., and BLOWSTEIN, M. I. The sedimentation time of the blood in jaundice. *J. Lab. & Clin. Med.*, 14:464-72, 1929.
1626. ROSS, G. R. Bilirubinaemia in malignant tertian malaria and black-water fever. *Brit. J. Exper. Path.*, 8:442-54, 1927.

1627. Rossi, A. Ricerche intorno all'azione della bile sui muscoli striati e sui nervi motori. *Atti del R. istituto Veneto sc. lett. arti*, 76:649-62, 1916-17.
1628. Rossi, A. Ricerche intorno all'azione della bile sul ricambio. *Arch. di farmacol. sper.*, Roma, 28:183-91, 1919.
1629. Rossi, A. Ricerche intorno all'azione della bile sulla eccitabilità dei centri di riflessione spinali. *Arch. per le sc. med.*, 43:156-66, 1920.
1630. Rost. Über instrumentelle Erweiterung der Papilla Vateri und Naht des Choledochus nach Choledochotomie. *Zentralbl. f. Chir.*, 54:20, 1927.
1631. Roszróczy, E. von. Über das Verhalten des freien und Ester-Cholesterins im Blute und in den Organen des Kaninchens bei künstlicher Gallenstauung. *Ztschr. f. d. ges. exper. Med.*, 68:690-700, 1929.
1632. Rothman, M. M.; Marenze, D. R.; and Marenze, T. Blood phosphatase as an aid in the differential diagnosis of jaundice. *Am. J. M. Sc.*, 192:526-35, 1936.
1633. Rous, P. Indicated differences in the reaction of the organs on vital staining with phthaleins. *J. Exper. Med.*, 41:739-59, 1925.
1634. Rous, P. Biliary aspects of liver disease. *Am. J. M. Sc.*, 170:625-31, 1925.
1635. Rous, P.; Broun, G. O.; and McMaster, P. D. The relation of carbohydrates to the output of bile pigment. *J. Exper. Med.*, 37:421-27, 1923.
1636. Rous, P., and Drury, D. R. Jaundice as an expression of the physiological wastage of corpuscles. *J. Exper. Med.*, 41:601-9, 1925.
1637. Rous, P., and Larimore, L. D. The biliary factor in liver lesions. *J. Exper. Med.*, 32:249-72, 1920.
1638. Rous, P., and McMaster, P. D. The concentrating activity of the gallbladder. *J. Exper. Med.*, 34:47-73, 1912.
1639. Rous, P., and McMaster, P. D. Physiological causes for the varied character of stasis bile. *J. Exper. Med.*, 34:75-95, 1921.
1640. Rousselot, L. M., and Bauman, L. The experimental production of cholesterosis of the gall bladder. *Surg. Gynec. Obst.*, 61:585-89, 1935.
1641. Rowntree, L. G.; Greene, C. H.; and Aldrich, M. Quantitative Pectenokof values in blood with special reference to hepatic disease. *J. Clin. Investigation*, 4:545-53, 1927.
1642. Royer, M. La Urobilina al estado normal y patológico. Tesis, Universidad nacional de Buenos Aires, 1929. Pp. 203.
1643. Royer, M. L'Urobiline à l'état normal et pathologique. Paris: Masson et Cie, 1930. Pp. 196.

1644. ROYER, M. Diminution de la bilirubine introduite dans l'intestin. *Compt. rend. Soc. de biol.*, 123:75-76, 1936.
1645. ROYER, M. Variations de la bilirubine sanguine et biliaire d'origine intestinale. *Compt. rend. Soc. de biol.*, 123:76-78, 1936.
1646. RUDBERG, H. Om traumatiska rupturer å gallgångarne. *Upsala läkaref. förh.*, 27:223-54, 1921-22.
1647. RUDOLPH, R. D., and COLE, C. E. C. The coagulation time of the blood in various diseases. *Am. J. M. Sc.*, 143:481-85, 1911.
1648. RUFFER, M. A., and CRENDIROPOULO, M. On the toxic properties of bile and on antihæmolytic serum. *J. Path. & Bact.*, 9:278-310, 1903-4.
1649. RUFFER, M. A., and CRENDIROPOULO, M. Substances favouring and inhibiting the action of hæmolysins of bile and serum. *Egypt. Sanit. Dept., Sci. Rep.*, 1906, pp. 129-39.
1650. RUFFER, M. A., and CRENDIROPOULO, M. Action de divers sels sur le pouvoir hémolytique de la bile in vitro. *Compt. rend. Soc. de biol.*, 60:260-61, 1906.
1651. RUFFER, M. A., and CRENDIROPOULO, M. Substances favouring and inhibiting on hæmolysins of bile and serum. *Lancet*, 11:70-73, 1907.
1652. RUFFIN, C. Ascite biliaire aiguë et péritonite biliaire aiguë sans perforation des voies biliaires. Lyon and Paris, 1913.
1653. RUSSEW, R. Das Eisen in der Galle und seine dissoziierte Retention. *Wien. Arch. f. inn. Med.*, 24:255-58, 1933.
1654. RUSZNYÁK, S. Studien über galletreibende Mittel. Die Wirkung des dehydrocholsäuren Natriums beim Menschen. *Ztschr. f. d. ges. exper. Med.*, 57:537, 1927.
1655. RUSZNYÁK, S., and BARÁT, I. Über den Mechanismus der Resistenzveränderung der roten Blutkörperchen. *Wien. Arch. f. inn. Med.*, 3:429-33, 1922.
1656. RUTHERFORD, W. On the physiological actions of drugs on the secretion of bile. From the Transactions of the Royal Society of Edinburgh, 29:1-263. Edinburgh: Neil & Co., 1879.
1657. RYÔ, K. Über die Gefässwirkung der Cholsäure. *Folia pharmacol., japon.*, 7:6, 1928.
1658. RYWOSCH, D. Vergleichende Versuche über die giftigen Wirkungen der Gallensäuren. *Arb. a. d. pharmak. Institut zu Dorpat*, 2:102, 1888.
1659. RYWOSCH, D. Über die giftige Wirkung der Gallensäuren nebst einem Anhang über die Giftigkeit der Gallenfarbstoffe (Bilirubin und Biliverdin). *Inaug. Diss. Dorpat*, 1891.
1660. RYWOSCH, D. Einige Notizen, die Giftigkeit der Gallenfarbstoffe betreffend. *Arb. d. pharmak. Institut zu Dorpat*, 8:157, 1891.

1661. RYWOSCH, D. Über die Galle des Meerschweinchens. *Centralbl. f. Physiol.*, 7:461, 1893-4.
1662. SAADI-NAZIM, M., and USUELLI, F. Influence des injections intra-veineuses de bile sur la sécrétion biliaire et sur la glycémie. *J. de physiol. et de path. gén.*, 25:43-50, 1927.
1663. SABADINI, I., and CURTILLET, E. Les Epanchements biliaires intra-peritonéaux sans perforation apparente des voies biliaires. *J. de chir.*, 45:191-232, 1935.
1664. SACKEY, M. S.; JOHNSTON, C. G.; and RAVDIN, I. S. Fate of bilirubin in the small intestine. *J. Exper. Med.*, 60:189-98, 1934.
1665. SAEKI, K. Studies in the photodynamic haemolytic action of bilirubin. *Jap. J. Gastroenterol.*, 4:153-65, 166-74, 231-54, 1932.
1666. SAEKI, K., and MAEDA, T. Experimental and clinical investigation on the affinity of bilirubin for erythrocytes. *Jap. J. Gastroenterol.*, 4:108-27, 255-61, 1932.
1667. SAIKI, S. Experimental investigation on the fate of bilirubin introduced into the blood vessels: changes of bilirubin concentration in the blood vessels and its limit of excretion into bile, urine and cerebro-spinal fluid. *Jap. J. Gastroenterol.*, 2:203-12, 1930.
1668. SAIKI, S. Jaundice in malarial disease: clinical and experimental investigations. *Jap. J. Gastroenterol.*, 3:46-53, 127-36, 1931.
1669. SAIKI, S. Experimental investigation on the fate of bilirubin introduced into the blood vessels. *Jap. J. Gastroenterol.*, 3:1-13, 119-22, 192-206, 1931.
1670. SAIKI, S. Clinical and experimental study on a dietetic therapy of the disease of gall-stone. *Jap. J. Gastroenterol.*, 5:79-83, 1933.
1671. SAITO, S.; SAKAI, K.; and SUZUKI, S. Acute intestinal obstruction. *Jap. J. Med. Sc.*, 1:43-56, 1927.
1672. SAKAMOTO, I., and FUJIKAWA, H. Eine Kritik der Nakagawa-Fujikawaschen Roten Mikrobestimmungsmethode der Gallensäure in der Galle. *J. Biochem.*, 13:309-19, 1931.
1673. SALANT, W. Some observations on the presence of albumin in the bile. *Proc. Soc. Exper. Biol. & Med.*, 3:78-80, 1905-6.
1674. SALKOWSKI, E. Taurins. *Chemisches Central-Blatt*, 3:No. 43, 646-47, 1872. *Deutsch. chem. Gesellschaft., Berlin*, 5:637-39, 1872.
1675. SALKOWSKI, E. Über die Entstehung der Schwefelsäure und das Verhalten des Taurins im thierischen Organismus. *Virchows Arch. f. path. Anat.*, 58:460-508, 1873. *Virchows u. Hirschs Jahresbericht*, 1:159, 1873.
1676. SALKOWSKI, E. Über die spontane Zersetzung des Bilirubins. *Ztschr. f. physiol. Chem.*, 12:227, 1887.
1677. SALKOWSKI, E. Zur Kenntnis der menschlichen Galle. *Berl. klin. Wchnschr.*, 54:63-64, 1917.

1678. SALMON, U. J. Excretion of bile pigments in experimental obstructive jaundice. *Surg. Gynec. Obst.*, 56:621-27, 1933.
1679. SAMELSON, S. Über gefäßverengernde und erweiternde Substanzen nach Versuchen an überlebenden Froschgefäßen. *Arch. f. exper. Path. u. Pharmacol.*, 66:347, 1911.
1680. SAMSON-HIMMELSTJERNA, J. V. Über leukämische Blut. Inaug. Diss. Dorpat, 1885.
1681. SANFORD, H. N.; CRANE, M. M.; and LESLIE, E. I. Bile salt hemolysis in new-born infants and its inhibition by blood serum. *Am. J. Dis. Child.*, 40:1039-44, 1930.
1682. SANNOMIYA, S. Biochemical studies on bile acids formation. *Sei-I-Kai M. J.* (abst. sect.), 55:5-6, 1936.
1683. SAPAREFF, M. Le Prurit dans l'ictère. Genève, 1912.
1684. SARAVIA, E. C.; MAZZOCCO, P.; and ROYER, M. Les Acides biliaires du sang après hépatectomie. *Compt. rend. Soc. de biol.*, 102:426-27, 1929.
1685. SAUNDERS, W. Abhandlung über die Structur der Leber. Leipzig, 1795.
1686. SAUNDERS, W. A treatise on the structure, economy, and diseases of the liver, together with an inquiry into the properties and component parts of the bile and biliary concretions. London: Walpole, 1810.
1687. SAVULESCU, A. Traitement de la syphilis par les arsénobenzols Bilies. *Soc. méd. des hôpitaux de Bucarest*, 7:220-27, 1930.
1688. SCHACK, O. Die Galle in ihrer Einwirkung auf die Herzthätigkeit. Inaug. Diss. Giessen, 1868. *Centralbl. f. d. med. Wissensch.*, 1868, p. 649.
1689. SCHÄFER, G. Die Erfolge der Chemotherapie mit gallensäuren Alkalien bei Puerperalfieber und bei gynäkologischen Streptokokkeninfektionen. *Deutsch. med. Wchnschr.*, 62:884-86, 1936.
1690. SCHAFFLER, J. Experimentelle Untersuchungen über Gallensekretion. *Ztschr. f. d. ges. exper. Med.*, 57:672-97, 1927.
1691. SCHEEL, O. Über den Nachweis von Gallenfarbstoff im Blutserum und dessen klinische Bedeutung. *Ztschr. f. klin. Med.*, 74:13-33, 1912.
1692. SCHEFFER, W. Ikterus, Hämorrhagien und Blutkoagulation. Inaug. Diss. (MS). Berlin, 1920.
1693. SCHEIFELE, J. Hämolyse und Gallensekretion am abgekühlten Tiere. Giessen, 1909.
1694. SCHIAPARELLI, P. Influenza del pH sulla tossicità taurocholato di sodio. *Riv. de clin. pediat.*, 31:461-64, 1933.
1695. SCHIFF, M. Über die Rolle des pankreatischen Saftes und der Galle bei Aufnahme der Fette. Moleschotts Untersuchungen, 2:345-56, 1857.

1696. SCHIFF, M. Gallenbildung, abhängig von der Aufsaugung der Gallenstoffe. *Arch. f. d. ges. Physiol.*, 3:598-624, 1870.
1697. SCHIFF, M. Acides biliaires. *Revue médicale de la Suisse*, 1881, No. 2.
1698. SCHIFF, M. Sur la réaction des acides biliaires et leur difference chez le bœuf et chez le cobaye. *Arch. f. d. ges. Physiol.*, 4:594-96, 1892.
1699. SCHINDEL, L. Eiweissbausteine und Gallensäurebildung. *Arch. f. exper. Path. u. Pharmakol.*, 168:38-48, 1932.
1700. SCHLÜNS, O. Vergleichende Untersuchungen über das Vorkommen von Gallenfarbstoff im Blute Schwangerer und Gebärender. *Zentralbl. f. Gynäk.*, 50:2185-88, 1926.
1701. SCHMIDT, F. C. Chemische und microscopische Untersuchungen über das Pfortader-Blut. *Hellers Archiv.*, 1846, pp. 487-520.
1702. SCHMIDT, A. Zur Blutlehre. Leipzig, 1892.
1703. SCHMIDT, A., and STRASBURGER, J. Die Fäzes des Menschen. Berlin, 1910.
1704. *SCHMIDT, C. L. A. The extra-hepatic functions of bile. *Physiol. Rev.*, 7:129-50, 1927.
1705. SCHMIDT, C. L. A.; ADELUNG, E. V.; and WATSON, T. On the elimination of taurin administered to man. *J. Biol. Chem.*, 33:501-3, 1918.
1706. SCHMIDT, C. L. A., and CLARK, G. W. The fate of certain sulfur compounds when fed to dogs. *J. Biol. Chem.*, 53:193-207, 1922.
1707. SCHMIDT, C. L. A., and DART, A. E. The estimation of bile acids in the bile. *J. Biol. Chem.*, 45:415-21, 1920.
1708. SCHMIDT, C. L. A., and WATSON, T. A method for the preparation of taurin in large quantities. *J. Biol. Chem.*, 33:499-500, 1918.
1709. SCHMIDT, C. R.; JONES, K. K.; and IVY, A. C. A method for the determination of the total pigment in bile which is applicable to "biliverdin biles." *Proc. Soc. Exper. Biol. & Med.*, 34:17-21, 1936.
1710. SCHMIDT, L. H. Further studies on the relation of thyroid activity to the power of certain bile salts to produce gastric ulcers. *J. Biol. Chem.*, 100:lxxxvi, 1933.
1711. SCHMIDT, L. H. The effect of thyroxine ingestion on the toxicity of certain bile salts. *Am. J. Physiol.*, 108:613-20, 1934.
1712. SCHMIDT, L. H. The rate of removal of bile salts from the blood as affected by thyroxine. *Am. J. Physiol.*, 116:138-39, 1936.
1713. SCHMIDT, R. Zur Stoffwechselfathologie des Icterus Catarrhalis und zur Frage der Paracholie. *Zentralbl. f. inn. Med.*, 19:113-28, 1898.
1714. SCHNEIDER, J. T. A study of the bile pigments in pernicious anemia. *J.A.M.A.*, 74:1759-64, 1920.

1715. SCHEONHOLZ, P., and MEYER, K. The influence of the H-ion concentration on the growth of *B. typhosus* in mediums containing bile or bile salt. *J. Infect. Dis.*, **28**:588-603, 1921.
1716. SCHOLDERER, H. Untersuchungen über die Resorption von Bilirubin aus dem Darm. *Biochem. Ztschr.*, **257**:145-50, 1933.
1717. SCHOLL, R. Über posttraumatische Hyperbilirubinämie, ein Beitrag zur Kenntnis der extrahepatalen Gallenfarbstoffbildung. *Arch. f. klin. Chir.*, **182**:127-32, 1935.
1718. SCHÖNHEIMER, R. Über die Resorptionbeschleunigung des Cholesterins bei Anwesenheit von Desoxycholsäure. *Biochem. Ztschr.*, **147**:258, 1924.
1719. SCHÖNHEIMER, R. Über die Bedeutung der Pflanzensterine für den tierischen Organismus. *Ztschr. f. physiol. Chem.*, **180**:1-37, 1929.
1720. SCHÖNHEIMER, R.; ANDREWS, E.; and HRDINA, L. Über das Auftreten ungekuppelter Gallensäuren in menschlicher Galle. *Ztschr. f. physiol. Chem.*, **208**:182-84, 1932.
1721. SCHOTTEN, C. Zur Kenntnis der Gallensäuren. *Ztschr. f. physiol. Chem.*, **10**:175-200, 1886.
1722. SCHOTTEN, C. Über die Säuren der menschlichen Galle. *Ztschr. f. physiol. Chem.*, **11**:268-76, 1887.
- 1723.*SCHRADER, M. E. G. Der hämatogene Ikterus. *Schmidts Jahrbücher*, **216**:73-108, 1887.
1724. SCHÜLEIN, M. Über die Einwirkung der Gallensäuren Salze auf den Verdauungskanal von Hunden. *Ztschr. f. Biol.*, **13**:172-92, 1877.
1725. SCHÜLER, L. Über Gallenrückfluss und seine Beziehung zu Mobilitätsstörungen des Magens nebst therapeutischen Bemerkungen. In *Beitr. z. klin. Med. Festschrift für Senator*, pp. 367-74. Berlin: A. Hirschwald, 1904.
1726. SCHULTE, E. Zur Frage der xanthelasmatischen Bildungen beim chronischen Ikterus. Freiburg, 1915. *Beitr. z. Path. Anat. u. z. allg. Pathol.*, **61**:570-88, 1916.
1727. SCHULTZ, W., and SCHEFFER, W. Über Ikterus, Haemorrhagien und Blutkoagulation. *Berl. klin. Wchnschr.*, **58**:789-94, 1921.
1728. SCHULTZ-BRAUNS, von O. Galle and Infektion. *Schweiz. med. Wchnschr.*, **57**:No. 36, 858, 1927.
1729. SCHULTZE, W. H. Zur Bakteriologie der operativ entfernten Gallenblasen. *Virchows Arch. f. path. Anat.*, **275**:717-22, 1929.
1730. SCHULTZEN, O., and NENCKI, M. Die Vorstufen des Harnstoffs im tierischen Organismus. *Ztschr. f. Biol.*, **8**:124-46, 1872.
1731. SCHÜPBACH, A. Über den Einfluss der Galle auf die Bewegung des Darmes. *Zentralbl. f. Physiol.*, **21**:365, 1907.

1732. SCHÜPBACH, A. Über den Einfluss der Galle auf die Bewegung des Dünndarms. *Ztschr. f. Biol.*, 51:1-41, 1908.
1733. SCHWANN, T. Versuche um auszumitteln, ob die Galle im Organismus eine für das Leben wesentliche Rolle spielt. *Arch. f. Anat., Physiol. u. wissenschaft. Med.*, 1844, pp. 127-59.
1734. SCHWARZ, E. The histology of destructive changes in icteric livers. *J. Path. & Bact.*, 25:207-12, 1922.
1735. SCHWARZ, H. Influence de l'administration de sucres sur la sécrétion biliaire. *Compt. rend. Soc. de biol.*, 116:1137-39, 1934.
1736. SCHWIEGK, H. Untersuchungen über die Leberdurchblutung und den Pfortaderkreislauf. *Arch. f. exper. Path. u. Pharmakol.*, 168: 693-714, 1932.
1737. SEIDEL, HANS. Permanente Gallenfistel und Osteoporose beim Menschen. *München. med. Wchnschr.*, 57:Part II, 2034, 1910.
1738. SEIFERT, E. Zur Frage der porotischen Malazie nach Gallen fisteln. *Beitr. z. klin. Chir.*, 136:496-98, 1926.
1739. SEKITOO, T. Über den Einfluss der Gallensäure auf die Salzausscheidung im Harn. *J. Biochem.*, 11:251-64, 1929; 12:251-64, 1930.
1740. SEKITOO, T. Über den Einfluss der Gallensäure auf den Calciumstoffwechsel. *J. Biochem.*, 11:391-406, 1929; 12:59-69, 1930.
1741. SELLARDS, A. W. The haemolytic action of bile and its inhibition by blood-serum. *Bull. Johns Hopkins Hosp.*, 19:268-71, 1908.
1742. SELLARDS, A. W. Ulceration of the stomach and necrosis of the salivary glands resulting from experimental injection of bile salts. *Arch. Int. Med.*, 4:502-9, 1909.
1743. SELLARDS, A. W. Mechanism of the reaction between bile salts and blood serum and the effect of conjugation in the formation of bile salts. *J. Exper. Med.*, 9:786-97, 1909.
1744. SELLARDS, A. W., and MINOT, G. R. Injection of hemoglobin in man and its relation to blood destruction, with especial reference to the anemias. *J. M. Research*, 34:469-79, 1916.
1745. SEMLER, R. Zur diuretische Wirkung der Gallensäuren. *Med. Klin.*, 22:891-92, 1926.
1746. SENAC, J. B. *Traité de la structure du cœur, de son action et de ses maladies*. Paris: J. Vincent, 1749.
1747. SENECA, LUCIUS ANNEUS. *Epistulae* 95, 16. *Omnia Opera*. Lipsiae: A. Justo, 1605.
1748. SÉNÈQUE, J., and TAILHEFER, A. Les Dilatations congénitales du cholédoque (anciens "kystes idiopathiques" du cholédoque). *J. de chir.*, 33:154-78, 1929.
1749. SENDJU, Y. Bildung der Blut- und Gallenfarbstoffe im bebrüteten Hühnerei. *J. Biochem.*, 7:191-96, 1927.

1750. SENNERT, D. *Epitome universam doctrinam summa fide complectens*, 1655, p. 681. BONETIUS (ed.). 1865.
1751. SEYDERHELM, R. Beziehungen der Galle zum Gesamtstoffwechsel. *Deutsche med. Wchnschr.*, **57**:305-7, 1931.
1752. SEYDERHELM, R., and TAMMANN, H. Die Gallenfistelanämie des Hundes. *Ztschr. f. d. ges. exper. Med.*, **57**:641-56, 1927.
1753. SEYDERHELM, R.; TAMMANN, H.; and BAUMANN, W. Über die Beeinflussung der Gallenfistelanämie durch Bestandteile der Galle. *Ztschr. f. d. ges. Med.*, **66**:539-56, 1929.
1754. SEYDERHELM, R., and TAMMANN, H. Über die Gallenfistelanämie des wachsenden Hundes und ihre Beeinflussung durch Kastration. *Ztschr. f. d. ges. exper. Med.*, **66**:557-65, 1929.
1755. SHAPIRO, A., and KOSTER, H. Influence of bile on excretion of sterol in the feces. *Am. J. Physiol.*, **116**:317-21, 1936.
1756. SHATTUCK, H. F.; KATAYAMA, I.; and KILLIAN, J. A. Bile pigments and bile acids of blood in jaundice. *Am. J. Med. Sc.*, **175**:103, 1928.
1757. SHATTUCK, H. F.; KILLIAN, J. A.; and PRESTON, M. A. Comparison of quantitative methods for the bilirubin of the blood. *J. Lab. & Clin. Med.*, **12**:802-10, 1927.
1758. SHEARD, C.; BALDES, E. J.; MANN, F. C.; and BOLLMAN, J. L. Spectrophotometric determinations of bilirubin. *Am. J. Physiol.*, **76**:577-85, 1926.
1759. SHEARD, C.; MANN, F. C.; and BOLLMAN, J. L. Spectrophotometric determinations of purified bilirubin. *Am. J. Physiol.*, **81**:774-81, 1927.
1760. SHELDON, L. B. A clinical study of biliary secretion in a case presenting completely obstructed common duct. *J.A.M.A.*, **104**:915-16, 1935.
1761. SHIBUYA, S. Über das Schicksal der Dehydrocholsäure in Hundeorganismus. *J. Biochem.*, **17**:159-62, 1933.
1762. SHIBUYA, S. Über das Schicksal der Dehydrocholsäure im Krötenorganismus. *J. Biochem.*, **17**:385-90, 1933.
1763. SHIBUYA, S., and TANAKA, T. Beiträge zur Kenntnis der Gallensäure aus der Fistelgalle des Kaninchens. *J. Biochem.*, **17**:391-93, 1933.
1764. SHIMIZU, T., and HATAKEYAMA, T. Über das Wachstumsvitamin A. *Ztschr. f. physiol. Chem.*, **182**:57-71, 1929.
1765. SHIMIZU, T., and ODA, T. Untersuchung der Krötengalle. Trioxybufosterocholensäure $C_{28}H_{46}O_5$ aus Wintergalle. *Ztschr. f. physiol. Chem.*, **227**:74-86, 1934.
1766. SHIONO, M. On the nature of the effect of the addition of salt upon the surface tension of sodium taurocholate solution. *J. Biochem.*, **12**:317-19, 1930.

1767. SHODA, M. Die Wasserstoffionenkonzentration bei der Fettspaltung durch Pankreassteapsin und Gallensäuren. Über das Verhältnis zwischen der Gallensäurenstruktur und der fettspaltenden Wirkung. *J. Biochem.*, 6:395-407, 1926.
1768. SHODA, M. Über die Ursodesoxycholsäure aus Bärengallen und ihre physiologische Wirkung. *J. Biochem.*, 7:505-17, 1927.
1769. SIBUYA, S. Über den Einfluss der Cholsäure auf die Milchsäureausscheidung bei blausäurevergifteten Kaninchen. *Biochem. Ztschr.*, 249:176-81, 1932.
1770. SIDEL, N., and ABRAMS, M. Jaundice in arthritis: its analgesic action. *N. E. Jour. Med.*, 210:181-82, 1934.
1771. SIEBER, E. Versuche über Einwirkung von Galle auf Bakterien und Protozoen. *Ver. Ges. D. Natf., Leipzig*, 1907-8, 79:551-52.
1772. SIEGMUND, E. Über die Gefahren bei operativen Eingriffen an den Gallenwegen und Mittel zu deren Bekämpfung mit Berücksichtigung der cholämischen Blutungen. *Deutsche Ztschr. f. Chir.*, 230:353-71, 1931.
1773. SIMMEL, H. Die Prüfung der osmotischen Erythrocytenresistenz. *Ergeb. d. inn. Med. u. Kinderh.*, 27:507-45, 1925.
1774. SIMNITZKY, S. Über den Einfluss der Gallenretention auf die secretorische Thätigkeit der Magendrüsens. *Berl. klin. Wchnschr.*, 38:1077, 1901.
1775. SIMON, F. *Animal chemistry* (Sydenham Soc. ed.), 1:43 and 106, 1845.
1776. SIMPSON, S. The relation between bile-secretion and bile-pressure. *Proc. Soc. Exper. Biol. & Med.*, 8:8-9, 1910.
1777. SINGER, G., and GLAESSNER, K. Die Wirkung der Gallensäuren auf die Darmeristaltik. *Verhandl. d. deutsch. Cong. inn. Med.*, 28:407-17, 1911.
1778. SINGER, G., and GLAESSNER, K. Die abführende Wirkung der Gallensäuren. *Arch. f. Verdauungskrankh.*, 18:192-210, 1912.
1779. SINGER, L. Die secretiones bilis. *Argentorati*, 1778.
1780. SJÖQVIST, J. [The composition of white bile.] Swedish. *Svenska läk. sällsk. handl.*, 42:1293-99, 1916.
1781. SKEETE, T. Case of considerable effusion of bile into the cavity of the abdomen in consequence of a fall; with the appearance on dissection and some additional remarks. *London M. J.*, 6:274, 1785.
1782. SKODA, M. *See* Shoda. 1767.
1783. SMITH, EAGLEFIELD. Observations and experiments on the digestive powers of the bile in animals. *London*, 1805. *European Magazine*, 31:386, 1797.

1784. SMITH, G. M. An experimental study of the relation of bile to ulceration of the mucous membrane of the stomach. *J. M. Research*, **30**:147-84, 1914.
1785. SMITH, H. P.; GROTH, A. H.; and WHIPPLE, G. H. Bile salt metabolism. *J. Biol. Chem.*, **80**:659-69, 671-84, 1928.
1786. SMITH, H. P., and WHIPPLE, G. H. Bile salt metabolism: casein, egg albumin, egg yolk, blood, and meat proteins as diet factors. *J. Biol. Chem.*, **89**:689-704, 1930.
1787. SMITH, H. P., and WHIPPLE, G. H. Bile salt metabolism: indene, hydrindene, and isatin. *J. Biol. Chem.*, **89**:719-25, 1930.
1788. SMITH, H. P., and WHIPPLE, G. H. Bile salt metabolism: Eck fistula modifies bile salt output. *J. Biol. Chem.*, **89**:738-51, 1930.
1789. SMITHIES, F. Parasitosis of the bile passages and gallbladder. *Am. J. M. Sc.*, **176**:225-53, 1928.
1790. SMYTH, F. S., and WHIPPLE, G. H. Influence of chloroform and phosphorus on bile fistula dogs. *J. Biol. Chem.*, **59**:623-36, 1924.
1791. SMYTH, F. S., and WHIPPLE, G. H. Bile salt metabolism: proteose and X-ray intoxication: thyroid and thyroxin. *J. Biol. Chem.*, **59**:637-46, 1924.
1792. SMYTH, F. S., and WHIPPLE, G. H. Bile salt metabolism: gelatin, fish, yeast, cod liver, and meat extracts. *J. Biol. Chem.*, **59**:647-54, 1924.
1793. SMYTH, F. S., and WHIPPLE, G. H. Bile salt metabolism: negative influence of drugs. *J. Biol. Chem.*, **59**:655-59, 1924.
1794. SNELL, A. M. The clinical application of recent studies on jaundice. *Surg. Gynec. Obst.*, **42**:528-35, 1926.
1795. SNELL, A. M. Changes in the proteins of blood in hepatic disease. *Proc. Staff Meet. Mayo Clinic*, **10**:489-92, 1935.
1796. SNELL, A. M. The effects of calculous biliary obstruction on the structure and functions of the liver. *Surg. Gynec. Obst.*, **63**:596-602, 1936.
1797. SNELL, A. M., and GREENE, C. H. The calcium in the serum in jaundice. *Am. J. Physiol.*, **92**:630-38, 1930.
1798. SNELL, A. M.; GREENE, C. H.; and ROWNTREE, L. G. A comparative study of certain tests for hepatic function in experimental obstructive jaundice. *Arch. Int. Med.*, **36**:273-91, 1925.
1799. SNELL, A. M.; GREENE, C. H.; and ROWNTREE, L. C. Further studies in experimental obstructive jaundice. *Arch. Int. Med.*, **40**:471-87, 1927.
1800. SNELL, A. M., and JORDAN, F. M. Some clinical features of obstructive jaundice. *Minnesota Med.*, **13**:699-707, 1930.

1801. SNELL, A. M., and KEYES, H. C. Pruritus of jaundiced patients: its incidence and treatment. *Med. Clin. N. Am.*, 16:1455-70, 1933.
1802. SNELL, A. M., and PLUNKETT, J. E. The hippuric acid test for hepatic function; its relation to other tests in general use. *Proc. Staff Meet. Mayo Clinic*, 10:638-39, 1935.
1803. SNELL, A. M., and ROWNTREE, L. G. Effects on bile of excessive amounts of water on the volume and composition of bile. *Am. J. Physiol.*, 85:577-90, 1928.
1804. SNELL, A. M.; VANZANT, F. R.; and JUDD, E. S. The complications and sequelae of prolonged obstructive jaundice. *Med. Clin. N. Am.*, 13:1417-38, 1930.
1805. SNIDER, F., and REINHOLD, J. G. A new interpretation of the van den Bergh reaction. *Am. J. M. Sc.*, 180:248, 1930.
1806. SOCOLOFF, N. Ein Beitrag zur Kenntnis der Lebersekretion. *Arch. f. d. ges. Physiol.*, 11:166, 1875.
1807. SOEJIMA, S. Klinische und experimentelle Untersuchungen über die cholämische Blutung. *Deutsche Ztschr. f. Chir.*, 212:217, 1928.
1808. SOFUE, N. Studies on the cause of the existence of two types of van den Bergh's reaction on bilirubin. *Jap. J. Med. Sc.*, 3:137-72, 1929.
1809. SOHN, A. Tödliche gallige Peritonitis nach Punktion des Chole-dochus. *Zentralbl. f. Chir.*, 52:2578-81, 1925.
1810. SOPHOCLES. *Frag.* 733.
1811. SPALLITTA, F. Azione della bile sui movimenti del cuore, ricerche. *Arch. per la sc. med.*, 11:107-21, 1887.
1812. SPALLITTA, F. Wirkung der Galle auf die Herzbewegung. *Moleschotts Untersuchungen*, 14:44-58, 1892.
1813. SPENCE, J. C., and OGILVIE, A. G. Cholemia, nervous symptoms in liver atrophy. *Arch. Dis. Child.*, 2:41, 1927.
1814. SPENCER, O. R. Do phosphatids interfere with bile salt determination? Master's thesis, University of Cincinnati, 1930.
1815. SPERRY, W. M., and STOYANOFF, V. A. The influence of sodium glycocholate on the enzymatic synthesis and hydrolysis of cholesterol esters in blood serum. *J. Biol. Chem.*, 117:525-32, 1937.
1816. SPIRO, P. Über die Gallenbildung bei Hunde. *Arch. f. Anat. u. Physiol.*, 1880, Suppl. B, pp. 50-94.
1817. SRIBHISHAJ, K.; HAWKINS, W. B.; and WHIPPLE, G. H. Bile pigment and hemoglobin interrelation in normal dogs. *Am. J. Physiol.*, 96:449-62, 1931.
1818. STÄDELER, G. Über die Farbstoffe der Galle. *Moleschotts Untersuchungen*, 9:395-422, 1863.
1819. STÄDELER, G. Über die Farbstoffe der Galle. *Ann. d. Chem.*, 132:323, 1864.

1820. STÄDELER, G., and FRERICH, F. T. Über das Vorkommen von Leucin und Tyrosin im thierischen Organismus. Mitt. d. naturf. Gesellsch., Zurich, 4:80-100, 1856.
1821. STÄDELER, G., and FRERICH, F. T. Über die Umwandlung der Gallensäuren in Farbstoffe. Mitt. d. naturf. Gesellsch., Zurich, 4:100-108, 1856. Arch. f. Anat., Physiol. u. wissensch. Med., 1856, pp. 55-61.
1822. STADELMANN, E. Weitere Beiträge zur Lehre vom Icterus. Deutsches Arch. f. klin. Med., 43:527-42, 1888.
1823. *STADELMANN, E. Der Icterus und seine verschiedenen Formen. Stuttgart: Enke, 1891.
1824. STADELMANN, E. Über den Kreislauf der Galle im Organismus. Deutsche med. Wchnschr., 22:787, 1896.
1825. STADELMANN, E. Über Chologoga. Berl. klin. Wchnschr., 33:212-15, 1896.
1826. *STADELMANN, E. Über den Kreislauf der Galle in Organismus. Ztschr. f. Biol., 34 (N.F. 16):1-64, 1896.
1827. STANOJEVIĆ, B., and ANDRIĆ, O. Die diuretische Wirkung der gallensäuren Salze. München. med. Wchnschr., 82:416-18, 1935.
1828. STANOJEVIĆ, L., and PETROVIĆ, S. Das Verhalten des Gallenfarbstoffspiegels im Blut bei intensiver Muskelarbeit. Klin. Wchnschr., 14:1146-47, 1935.
1829. STEINER, J. Zur Innervation des Froschherzens. Arch. f. Anat., Physiol. u. wissensch. Med., 1874, pp. 474-90.
1830. STEINER, R. Vier Fälle von sogenannter "weisser Galle." Wien. klin. Wchnschr., 27:975-78, 1914.
1831. STEINHAUS, J. Über die Folgen des dauernden Verschlusses des Ductus Choledochus. Arch. f. exper. Path. u. Pharmakol., 28:432-49, 1891.
1832. STEKOL, J. A., and MANN, F. C. The role of bile in the absorption and detoxification of bromobenzene and naphthalene in the dog. J. Biol. Chem., 117:619-27, 1937.
1833. STENGEL, A. Diseases of the liver and gallbladder. In NELSON, Loose leaf living medicine, 5:471-530B, 1927.
1834. STERLING, S. Experimentelle Beiträge zur Pathogenese des Icterus mit spezieller Berücksichtigung der Gallencapillaren. Inaug. Diss. Breslau, 1911.
1835. STERN, R. Über die klinische Bedeutung des Cholesterins in der Galle und im Blutserum. Breslau: Habilitationschrift, 1926.
1836. STERNER, R.; BARTLE, H.; and LYON, B. B. V. The chologogue effect of the intravenous injection of sodium dehydrocholate, with a résumé of literature on bile salt metabolism. Am. J. M. Sc., 182: 822-39, 1931.

1837. STEWART, G. N. The effect of electrolysis and of putrefaction on the bile and particularly on the bile pigments. *Stud. Physiol. Lab., Owens Coll., Manchester*, 1:201-6, 1891.
1838. STEWART, H. L., and CANTAROW, A. Decompression of the obstructed biliary system of the cat. *Am. J. Digest. Dis. & Nutrition*, 2: 101, 1935.
1839. STEWART, H. L., and LIEBER, M. M. Hepatic changes associated with decompression of obstructed biliary passages. *Arch. Path.*, 18: 30-41, 1934.
1840. STILL, E. U. Toxicity of purified bile products. *Proc. Inst. Med. Chicago*, 7:179, 1929.
1841. STILL, E. U. On the toxicity of purified bile preparations. *Am. J. Physiol.*, 88:729-36, 1929.
1842. STILL, K. S., and CARLSON, A. J. The motor and secretory activity of the stomach during acute and chronic obstructive jaundice in dogs. *Am. J. Physiol.*, 80:34-44, 1929.
1843. ST. JOHN, F. B. Late results of biliary fistula with implantation of fistulous tract into stomach. *Ann. Surg.*, 83:855-57, 1926.
1844. STOKVIS, B. J. Diss. continens quaedam de glucogenesi in hepate. (Dutch text.) Utrecht: J. V. Schattenkerk, 1856. Pp. 72. Amsterdam: Onderz. Phys. Lab., 1:1856-57.
1845. STOLNIKOFF, J. Über die Wirkung der Galle auf die Fäulniss von Fibrin und Fett. *Ztschr. f. physiol. Chem.*, 1:343-44, 1877-78.
1846. STRAIN, W. H., and MARSCH, M. E. The effect of bile salts on the oxygen consumption of dog tissues. *Am. J. Physiol.*, 115:82-89, 1936.
1847. STRANSKY, E. Über die Wirkung von Salzen auf die Gallensekretion. Weitere Untersuchungen über die Pharmakologie der Gallensekretion. *Biochem. Ztschr.*, 143:438-56, 1923; 155:256-98, 1925.
1848. STRANSKY, E. Untersuchungen über die Pharmakologie der Gallensekretion; Ausscheidung von Stoffen durch die Galle. *Ztschr. f. d. ges. exper. Med.*, 77:807-41, 1931.
1849. STRAUS, D. C., and HAMBURGER, W. W. The significance of cardiac irregularities in reference to the operability of cases of cholelithiasis, cholecystitis, and duodenal ulcer. *J.A.M.A.*, 82:706, 1924.
1850. STRAUSS, H. Über den osmotischen Druck der menschlichen Galle. *Klin. Wchnschr.*, 40:261-64, 1903.
1851. STRAUSS, H. Über die Resistenz der roten Blutkörperchen beim Ikterus. Diss. Strassburg: Druckerei, 1908.
1852. STRECKER, A. Untersuchung der Ochsen-galle. *Ann. d. Chem.*, 65: 1-37, 1848; 67:1-60, 1848.
1853. STRECKER, A. Untersuchungen über chem. Constitution der Hauptbestandtheile der Ochsen-galle. Giessen: Habilitationsschrift, 1848.

1854. STRECKER, A. Beobachtungen über die Galle verschiedener Thiere. *Ann. d. Chem.*, 70:149-98, 1849.
1855. SUGANO, D. M. Ein Versuch über die Gallensäurenausscheidung bei einem Fall von Cholelithiasis mit Gallenblasenfistel. *J. Biochem.*, 7:457-71, 1927.
1856. SUGIŪ, Y. Changes of the bile in fever. *Jap. J. Gastroenterol.*, 2: 111, 1930.
1857. SURMONT, M. Recherches sur la toxicité urinaire dans les maladies du foie. *Compt. rend. Soc. de biol.*, 44:23-27, 1892.
1858. SYDENHAM, THOMAS. *Opera omnia*, iv. 7 (Greenhill ed., pp. 194-203). Londini, 1846.
1859. SZILARD, P. Eine neuere kolorimetrische Methode zur quantitativen Bestimmung der gallensäuren Salze im Blute. *Biochem. Ztschr.*, 153:440, 1926.
1860. SZÖRÉNYI, E. Die Löslichkeit der Fettsäuren in Galle unter Einwirkung des Lecithins. *Biochem. Ztschr.*, 249:182-88, 1932.
1861. SZYMÁNSKA, J. [Inhibitive action of bile on growth of *H type Proteus vulgaris*.] Polish. *Med. doświadcz. i społ.*, 13:234-38, 1931.
1862. TADA, Y. Ausscheidung durch Leber und Niere. Experimentelle Untersuchungen. *Jap. J. Gastroenterol.*, 5:143-86, 1933.
1863. TADA, Y. Experimentelle Untersuchung über die Ausscheidungstelle der Farbstoffe in der Leber. *Jap. J. Gastroenterol.*, 5:191-200, 1933.
1864. TADA, Y., and HISHIKAWA, K. Über die Beziehungen zwischen den chemischen Konstitutionen und der Ausscheidung der Farbstoffe aus Leber und Niere. *Jap. J. Gastroenterol.*, 5:187-90, 1933.
1865. TAFURI, G. [Effects of bile in general and cholesterol in particular, on kidney.] *Gaz. internaz. med. chir.*, 38:595-608, 1930.
1866. TAKÁCS, L. Der Einfluss des Sekretin auf die Gallenabsonderung und auf die diabetische Acidose. *Ztschr. f. d. ges. exper. Med.*, 62: 114-17, 1928.
1867. TAKAHASHI, C. Significance of pigments in the treatment of infection of the bile ducts. *Jap. J. Gastroenterol.*, 6:7-9, 1934.
1868. TAKAHASHI, S. Experimentelle Untersuchungen über die Beeinflussung der Gallenabsonderung durch Uterustonicae. *J. Orient Med.*, 12:11, 1930.
1869. TAKAKI, T. Über das Vorkommen der Aminosäuren in der Galle der Choledochuscyste. *J. Biochem.*, 6:27-29, 1926.
1870. TAKASHIMA, M. Über den Einfluss von Körpersäften auf die Blutgerinnung; über den Einfluss der Galle auf die Gerinnung des Blutes. *Acta scholae med. univ. imp. in Kioto*, 16:214-20, 1933.
1871. TAKATA, H. Über den Einfluss der Gallensäure auf Glycerophosphatase. *J. Biochem.*, 14:61-67, 439-45, 1931.

1872. TAKATA, H. Einfluss der Gallensäure auf die enzymatische Spaltung von Lecithin. *J. Biochem.*, 18:63-74, 1933.
1873. TAKU, A. Hypoglykämische Wirkung der Gallensäure. *J. Biochem.*, 9:299-319, 1928.
1874. TAKU, A. Die Wirkung der Cholsäure auf die Kreatininausscheidung bei Zufuhr verschiedener vegetativer Nervengifte. *J. Biochem.*, 13:237-54, 1931.
1875. TALMA, S. Von der baktericiden Wirkung der Galle. *Ztschr. f. klin. Med.*, 42:354-70, 1901.
1876. TAMMANN, H. Untersuchungen über Rachitis und Osteomalazie. *Jena*, 1910.
1877. TAMMANN, H. Über die Beeinflussung der parotischen Osteomalazie nach Gallenfistel durch das D-Vitamin. *Beitr. klin. Chir.*, 142:83-120, 1928.
1878. TANAKA, K. Beiträge zur Kenntnis der hypoglykämischen Wirkung der Gallensäure. *J. Biochem.*, 14:463-73, 1932.
1879. TANAKA, K. Über die Gallensäure der Löwengalle. *Ztschr. f. physiol. Chem.*, 213:199-200, 1932.
1880. TANAKA, K. Keimdrüsenautolyse unter dem Einfluss der Gallensäure. *J. Biochem.*, 17:111-16, 1933.
1881. TANAKA, K., and TANAKA, T. Über die Gallensäurebildung. Reiseum- und Gallensäureausscheidung. *J. Biochem.*, 18:15-22, 1933.
1882. TANAKA, T. Die Bedeutung der Gallensäure im Kohlehydratstoffwechsel. *J. Biochem.*, 18:33-43, 1933.
1883. TANAKA, T. Einfluss der Milz auf die Gallen- und Gallensäureausscheidung. *J. Biochem.*, 18:369-77, 1933.
1884. TANAKA, T. Über Taurocholsäure. *Ztsch. f. physiol. Chem.*, 220:39-42, 1933.
1885. TAPPEINER, H. Über die Aufsaugung der Gallensäuren Alkalien im Dünndarme. *Sitzungsber. d. Kaiserl. Akad. d. Wissensch.*, 3:1-5, 1878.
1886. TAPPOLET, A. Zur Herzwirkung der Gallensäuren. *Schweiz. med. Wchnschr.*, 52:1210, 1922.
1887. TARCHANOFF, J. T. Über die Bildung von Gallenpigment aus Blutfarbstoff im Thierkörper. *Arch. f. d. ges. Physiol.*, 9:53-65, 1874.
1888. TARCHANOFF, JOHANNES (PRINCE). Zur Kenntnis der Gallenfarbstoffbildung. *Arch. f. d. ges. Physiol.*, 9:329, 1874.
1889. TARR, L.; OPPENHEIMER, B. S.; and SAGER, R. V. The circulation time in various clinical conditions determined by the use of sodium dehydrocholate. *Am. Heart J.*, 8:766-86, 1933.

1890. TASHIRO, S. Determination of bile salts in the blood. *Cincinnati J. Med.*, 4:197, 1923.
1891. TASHIRO, S. Nature and amount of bile salts in normal blood. *Am. J. Physiol.*, 90:538-39, 1929.
1892. TASHIRO, S. Nature and amount of bile salts in the normal blood. Abstracts & Communication of the XIIIth Internat. Physiol. Cong. Boston, Aug., 1929, pp. 267-68.
1893. TASHIRO, S. Are there any bile salts in normal blood? *Med. Bull. Univ. Cincinnati*, 6:40-50, 1931.
1894. TASHIRO, S., and LEE, O. L. Note on the "antagonistic action" of glycerol toward bile salts in blood coagulation. *Med. Bull. Univ. Cincinnati*, 6:90-97, 1931.
1895. TASHIRO, S., and MILLS, C. A. Note on the antagonistic action of cholesterol to the bile salts in blood coagulation. *Med. Bull. Univ. Cincinnati*, 6:98-99, 1931.
1896. TASHIRO, S., and OLIVER, S. Note on antagonistic power of glycerol and cholesterol to bile salts in gastric ulcer formation. *Med. Bull. Univ. Cincinnati*, 6:100-101, 1931.
1897. TASHIRO, S., and SCHMIDT, L. H. Note on reciprocal relationship between blood sugar and Pettenkofer positive substances in blood in intestinal obstruction. *Med. Bull. Univ. Cincinnati*, 6:84-89, 1931.
1898. TASHIRO, S., and SCHMIDT, L. H. The relation of thyroid activity to the production of gastric ulcer by bile salts. *Med. Bull. Univ. Cincinnati*, 6:137-43, 1931.
1899. TASHIRO, S., and SCHMIDT, L. H. A preliminary report on the relation of blood phospholipids to experimental gastric ulcer (bile salts). *Med. Bull. Univ. Cincinnati*, 6:144-50, 1931.
1900. TASHIRO, S., and SCHMIDT, L. H. The effect of the administration of bile salts on Pettenkofer positive substances and lipid phosphorus content of the blood. *Med. Bull. Univ. Cincinnati*, 6:151-55, 1931.
1901. TASHIRO, S.; SCHMIDT, L. H.; and TIETZ, E. B. Quantitative studies on the Pettenkofer reaction of different lipids and of blood filtrate. *Med. Bull. Univ. Cincinnati*, 6:62-73, 1931.
1902. TASHIRO, S.; TIETZ, E. B.; and TANGE, U. Quantitative studies on the Pettenkofer reaction of different bile salts and of blood filtrate. *Med. Bull. Univ. Cincinnati*, 6:51-61, 1931.
1903. TATEISHI, C. Die Zuckerausscheidungsschwelle unter dem Einfluss der Cholsäure und der Milz. *J. Biochem.*, 19:409-23, 1934.
1904. TATEISHI, C. Die Z.A.S. Gallenblasenfistelkaninchen unter Einfluss des Milzextraktes und der Gallensäure. *J. Biochem.*, 21:55-62, 1935.

1905. TATUM, A. L. The influence of bile on autolysis. *J. Biol. Chem.*, **27**: 243-48, 1916.
1906. TAYLOR, N. B.; WELD, C. B.; and SYKES, J. F. The relation of bile to the absorption of vitamin D. *Brit. J. Exper. Path.*, **16**:302-9, 1935.
1907. TEEPLE, J. E. On bilirubin, the red coloring matter of the bile. Ph.D. Diss., No. 45, Cornell University, 1903.
1908. TENEFF, S. La Funzionalità epatica in rapporto all'intervento ed all'anestesia, nelle malattie chirurgiche in genere, nelle affezioni e nel drenaggio delle vie biliari. *Arch. ital. di chir.*, **39**:221-300, 1935.
1909. TERAOKA, M. Experimental study of influence of bile on secretion movement of alimentary canal. *Bull. Nav. M. A., Japan (abst. sect.)*, **25**:21-22, 32-34, 1936.
1910. TERAOKA, M. Über die Kenntnis von der Fischgalle. *J. Biochem.*, **8**:341-49, 1928.
1911. TERAOKA, M. Über den Einfluss der Gallensäure auf den Milchsäurestoffwechsel. *Biochem. Ztschr.*, **249**:95-117, 1931.
1912. TERAOKA, M. Über den Einfluss der Gallensäure auf die Blutglykolyse und die Glykogenolyse des Muskels. *Biochem. Ztschr.*, **249**: 118-25, 1932.
1913. TERESENKOV, N. M. [Post-operative icterus.] Russian. *Russ. chirurg. arch.*, St. Petersburg, **19**:442-60, 1903.
1914. TERRIER, F., and AUVRAY, M. Les Traumatismes du foie et des voies biliaires. *Rev. de chir., Paris*, **17**:16-38, 1897.
1915. THANNHAUSER, S. J. Über das Bilirubin. München, 1913.
1916. THÉNARD, L. J. Deux mémoires sur la bile, lus à l'Institut. *Mém. de phys. et de chim. de la Soc. d'Arcueil*, **1**:23, 1807.
1917. THENARD, L. J. Nouvelles expériences sur la bile. Dijon, Séances acad., 1823, pp. 26-29.
1918. THIÉBAUT, F. Epreuves biologiques dans les ictères. Paris: Masson et Cie, 1932. Pp. 192.
1919. THOMAS, E. Action des sels biliaires sur le développement de la bradycardie ictérique: étude expérimental. *Rev. méd. de la Suisse Rom.*, **50**:207-11, 1930.
1920. THOMAS, J. D. Upon the occasional presence of bilirubin in hydatid cysts. *Intercolon. M. Cong. Tr. Melbourne*, **2**:390-92, 1889.
1921. THOMAS, R. Über Abhängigkeit der Absonderung und Zusammensetzung der Galle von der Nahrung. Diss. Strassburg, 1890.
1922. THOMSON, E. M. The pathology and bacteriology of the liver and bile passages. *Royal Prince Alfred Hospital Year Book*, 1934, p. 42.
1923. THOMSON, J. Congenital obliteration of the bile ducts. In C. ALLBUTT and H. D. ROLLESTON, *System of medicine*, **4**:Part I, 106-9. London: Macmillan & Co., 1908.

1924. THOMSON, W. A practical treatise on the diseases of the liver and biliary passages. Philadelphia: Barrington & Geo. D. Haswell, 1842. Pp. 339.
1925. THORSNESS, E. T. Bacteriology of cholecystitis. Surg. Gynec. Obst., 59:752-55, 1934.
1926. THUDICHUM, J. L. W. Tenth Report of the Medical Officer of the Privy Council, London, 17:243, 1868.
1927. THURSTON, H. F. The rôle of toxin of *Bacillus welchii* in the toxemia of acute intestinal obstruction. Arch. Surg., 22:71-85, 1931.
1928. TIEDEMANN, F., and GMELIN, L. Die Verdauung nach Versuchen. Heidelberg and Leipzig: K. Groos, 1826.
1929. TIEDEMANN, F., and GMELIN, L. Recherches, expérimentales, physiologiques et chimiques sur la digestion. Jourdan's translation, Paris: 1827.
1930. TIETZ, E. B., and GOLDBLATT, S. Note on reciprocal relationship between blood sugar and Pettenkofer positive substances: in mercury poisoning. Med. Bull. Univ. Cincinnati, 6:74-83, 1931.
1931. TIPREZ, J., and DUMONT, Y. L'Ictère dans l'ulcère duodénal. Echo méd. du nord., 34:415, 1930.
1932. TISSIER, P. Essai sur la pathologie de la sécrétion biliaire. Thèse. Paris, 1889.
1933. TODA, R. Zur Frage von der Sterilität der Galle unter normalen Verhältnissen und über ihre baktericide Wirkung auf pathogene Bakterien. Arch. f. klin. Chir., 103:407-39, 1914.
1934. TOMINAGA, Y. Untersuchungen über die Beziehungen zwischen Gallenabsonderung und Eierstöcken. Biochem. Ztschr., 157:126-45, 1925.
1935. TOMMASELLI, A. Ricerche sulla azione de colato di sodio sulla funzione motoria dell'utero. Riv. di pat. sper., 5:522-26, 1930.
1936. TOMOZAWA, T. Über die Veränderung der Pankreaszellen, die durch Galle oder Gallensäure hervorgerufen wird. Okayama-Igakkai-Zasshi, 46:1027, 1934.
1937. TOMOZAWA, T. Über die Wirkung der Galle oder der Gallensäure auf die Herzmuskulatur. Okayama-Igakkai-Zasshi, 46:1034, 1934.
1938. TOMOZAWA, T. Über die Veränderung der Ganglienzellen, die infolge der Galle oder Gallensäure auftritt. Okayama-Igakkai-Zasshi, 46:1253, 1934.
1939. TRAUBE, L. Über den Einfluss der gallensäuren Salze auf die Herzthätigkeit. Berl. klin. Wehnschr., 1:Part I, 85-87, 145-47, 1864. Gesammelte Beiträge, Berlin, 1:366, 1871.
1940. TREVES, F. A case of jaundice of sixteen years' standing treated by operation. Practitioner, 62:18-20, 1899.

1941. TRINCAS, M. Gli effetti dei sali biliari sulla motilità intestinale. *Gior. di clin. med.*, **14**:346-51, 1933.
1942. TROIN, G. Hemolyse et cholémie expérimentales chez le chien. *Compt. rend. Soc. de biol.*, **60**:121-23, 1906.
1943. TROISIER, J. Rôle des hémolysines dans la genèse des pigments biliaires et de l'urobiline. Thèse. Paris, 1910.
1944. TRUSLER, H. M., and REEVES, J. R. Significance of anaerobic organisms in peritonitis due to liver autolysis: bacterial flora of the liver and muscle of normal dogs. *Arch. Surg.*, **28**:479-91, 1934.
1945. TRUSLER, H. M., and REEVES, J. R. Significance of anaerobic organisms in peritonitis due to liver autolysis: a bacterial study of the peritoneal exudates. *Arch. Surg.*, **30**:371-93, 1935.
1946. TSCHOPP, E. Über Rückresorption im Tierkörper. *Protoplasma*, **6**:70-83, 1929.
1947. TSUJI, K. Über den Mechanismus der hypoglykämischen Wirkung der Gallensäure. *J. Biochem.*, **12**:139-60, 1930.
1948. TSURUTA, T. Antagonistic action of lipids to bile salts in gastric ulcer formation. *Med. Bull. Univ. Cincinnati*, **6**:110-16, 1931.
1949. TSURUTA, T. Antagonistic action of various lipids to bile salts on frog muscle. *Med. Bull. Univ. Cincinnati*, **6**:117-23, 1931.
1950. TSURUTA, T. Further studies on antagonistic action of lipids to the toxic action of the bile salts. *Med. Bull. Univ. Cincinnati*, **6**:124-29, 1931.
1951. TSURUTA, T. Relationship of sex to susceptibility to the toxicity of bile salts. *Med. Bull. Univ. Cincinnati*, **6**:134-36, 1931.
1952. TUZIOKA, S. Bedeutung der Gallensäure in Kalkstoffwechsel. Kalkausscheidung im Harn und Galle bei normalem sowie thyreoparathyreoideaprimem Hunde. *J. Biochem.*, **21**:219, 1935.
1953. TUZIOKA, S. Bedeutung der Gallensäure im Calciumstoffwechsel, Kalkausscheidung in der Galle und im Harn der thyreoparathyreopriven Hündin bei Zufuhr von Cholsäure und Thyreoparathyreoideaextrakt. *J. Biochem.*, **22**:123-37, 1935.
1954. TUZIOKA, S. Über den Einfluss der Thyreoparathyreoidektomie und der Gallensäure auf die Gallensäureausscheidung und auf das pH der Galle bei Gallenistelhunden. *J. Biochem.*, **22**:367-74, 1935.
1955. UDRANSZKY, L. Über die Beziehung, im Harn bereits vorgebildeten, oder daraus durch einfache Procedures darstellbaren Farbstoffe zu den Huminsubstanzen. *Ztschr. f. physiol. Chem.*, Strassburg, **11**:537-60, 1887.
1956. UMBER, F. Erkrankungen der Leber und der Gallenwege. Handbuch der inneren Medizin. Berlin: Julius Springer, 1918.
1957. UNVERRICHT, D. W., and FREUDE, D. E. Die Wirkung intravenöse Injektionen auf das Magenbild. *Klin. Wchnschr.*, **6**:1658, 1927.

1958. URAKI, Z. Über den Einfluss der Gallensäure auf die Synthese und Spaltung der Hexosephosphorsäure in der Leber, der Niere und im Muskel. *J. Biochem.*, 14:123-44, 1931.
1959. URAKI, Z. Photobiologische Eigenschaften der Gallensäure. Bildung der β -Cholsäure aus Cholsäure durch Ultraviolettstrahlen. *Ztschr. f. physiol. Chem.*, 207:16-24, 1932.
1960. URAKI, Z. Bedeutung der Gallensäure in Kohlehydratstoffwechsel. *J. Biochem.*, 18:207-25, 1933.
1961. USUKI, K. An experimental study on the influence of a diet upon the formation of hepatic and renal calculi. *Jap. J. Gastroenterol.*, 6:94-104, 1934.
1962. USUKI, K. On the changes of hydrogen ion concentration and the buffer action of the bile. *Jap. J. Gastroenterol.*, 6:105-11, 1934.
1963. VACCARO, P. F. The synthesis of hippuric acid, its value in detecting hepatic damage secondary to diseases of the extrahepatic biliary system. *Surg. Gynec. Obst.*, 61:36-41, 1935.
1964. VALDONI, P. Studi sul potere di assorbimento della cistifellea normale e patologicamente alterata: genesi della bile bianca e produzione sperimentale di calcoli biliari. *Policlinico*, 38:140-50, 1931.
1965. VALENTINER, W. Zur Kenntniss der animalischen Pigmente. *Virchows Arch. f. path. Anat.*, 17:200-202, 1859.
1966. VALENTINER, W. Ein Beitrag zur Lehre von Farbstoffen und Chromogenen des Organismus. *Reichert's Archiv.*, 1862, pp. 773-77.
1967. VAN DEN BERGH, A. A. H. Der Gallenfarbstoff im Blute. *Leiden: S. C. van Doesburgh*, 1918. Pp. 111.
1968. VAN DEN BERGH, A. A. H. La Recherche de la bilirubin dans le plasma sanguin. *Presse méd.*, 29:441-43, 1921.
1969. VAN DEN BERGH, A. A. H. Discussion on jaundice. *Brit. M. J.*, 2: 498-500, 1924.
1970. VAN DEN BERGH, A. A. H.; GROTEPASS, W.; and REVERS, F. E. Beitrag über das Porphyrin in Blut und Galle. *Klin. Wchnschr.*, 11: 1534-36, 1932.
1971. VAN DEN BERGH, A. A. H., and MÜLLER, P. Über eine direkte und eine indirekte Diazoreaktion auf Bilirubin. *Biochem. Ztschr.*, 77: 90-103, 1916.
1972. VAN DEN BERGH, A. A. H., and SNAPPER, J. Die Farbstoffe des Blutserums. *Deutsches Arch. f. klin. Med.*, 110:540-61, 1913.
1973. VAN DEN BERGH, A. A. H., and SNAPPER, J. Untersuchungen über den Icterus. *Berl. klin. Wchnschr.*, 51:1109-82, 1914.
1974. VAN DEN VELDEN. Icterus gravidarum. *Hegars Beitr. z. Geburtsh. u. Gynäk.*, 8:448, 1904.
1975. VAN HELMONT, JAN BAPTISTA. *Scholarum humoristarum passiva de ceptio atque ignorantia*, p. 72. *Amstelodami*, 1648.

1976. VANNINI, G. Ikterus und Stoffwechsel. *Ztschr. f. klin. Med.*, **75**: 136-42, 1912.
1977. VAN REVERHORST, M. De motu bilis circulari ejusque morbis. *Lugd. Bat.*, 1722.
1978. VAQUEZ, H. Resistance du sang dans l'ictère et au cours de l'immunisation contre le taurocholate de soude. *Compt. rend. Soc. de biol.*, **56**: 565-66, 1904.
1979. VAQUEZ, H. Diseases of the heart. G. F. LAIDLAW (tr.). Philadelphia: W. B. Saunders Co., 1924.
1980. VARELA FUENTES, B.; APOLO, E.; and ESCULIES, J. Veränderungen der Gallensalz-, Bilirubin-, und Cholesterinwerte im Blute des Hundes bei experimentellem Obstruktionsikterus. *Ztschr. f. d. ges. exper. Med.*, **73**: 412-21, 1930.
1981. VARELA, F. B., and RUBINO, M. C. Capacité d'absorption du sérum sanguin pour la bilirubine pure. *Compt. rend. Soc. de biol.*, **111**: 527-31, 1932.
1982. VASILENKO, N. L. [Concerning the functional disturbance of the kidney by retention of bile.] Russian. Diss. St. Petersburg, 1907.
1983. VENULET, F. Influence de la bile de bœuf sur l'infection des rats blancs par le bacille paratyphique B. *Compt. rend. Soc. de biol.*, **93**-1: 366-67, 1925.
1984. VERBITSKI, M. K. [On the influence of bile pigments upon the organism in retention of bile.] Russian. St. Petersburg, 1895.
1985. VERZÁR, F. Die Rolle des Bilirubins bei der Regulation der roten Blutkörperchenzahl. *Ztschr. f. d. ges. exper. Med.*, **68**: 475-81, 1929.
1986. VERZÁR, F.; ÁRVAY, A. VON; PETER, J.; and SCHOLDERER, H. Serum-Bilirubin und Erythropoëse im Hochgebirge. *Biochem. Ztschr.*, **257**: 113-29, 1933.
1987. VERZÁR, F., and ZIH, A. Bilirubin als ein mögliches hämopoëtisches Hormon. *Klin. Wchnschr.*, **7**: 1032, 1928.
1988. VERZÁR, F., and ZIH, A. Die hämopoëtische Wirkung von Bilirubin und anderen Hämoglobinderivaten. *Biochem. Ztschr.*, **205**: 388-401, 1929.
1989. VETRANO, G. Azione batteriolitica ed antitossica della bile. *Ospedale, Palermo*, **2**: 383-87, 1909. *Centralbl. Bakt.*, Jena, **1**. Abt., **52**: 275-86, 1909.
1990. VILIZHANIN, P. [Physiological and pathological effect of bile under certain conditions.] Russian. *Ejened. klin. gaz. St. Peterburg*, **6**: 569, 589, 625, 642, 1886.
1991. VILLENEUVE, M. Ictère. *Dictionaire des sciences médicales*, **23**: 386-463, 1818.

1992. VILLETTE, R. La Metamorfosi regressiva nelle malattie del fegato in rapporto alla tossicità dell'urina. *Istituto di farmacologia sperimentale*, 3:75-110, 1896.
1993. VINCENT, H. Action de la bile sur la toxine tétanique. *Compt. rend. Soc. de biol.*, 63:623-25, 1907.
1994. VINCENT, H. Deuxième note sur les propriétés antitoxiques de la bile: action des éléments composants de la bile sur la toxine tétanique. *Compt. rend. Soc. de biol.*, 63:695-97, 1907.
1995. VINCENT, H. Action antiseptique de la bile sur le toxines microbiennes de l'intestin. *Presse méd.*, 17:927, 1909.
1996. VINCENT, H. Sur les cryptotoxines biliaires. *Comptes rend. Soc. de biol.*, 95:1525-26, 1926.
1997. VIOLA, G., and TARUGI, B. La Influenza della bile sulle resistenze dei globuli rossi. *Riforma med.*, 18:Part III, 771-83, 1902.
1998. VIRCHOW, R. Zur pathologischen Physiologie des Bluts—Pigmentierte. *Virchows Arch. f. path. Anat.*, 2:587-98, 1842.
1999. VIRCHOW, R. Die pathologischen Pigmente. *Virchows Arch. f. path. Anat.*, 1:379-486, 1847.
2000. VIRGIL. *Aeneid* xii. 857.
2001. VOGEL, R. Über gallige Peritonitis. *Wien. klin. Wchnschr.*, 26: 1153-57, 1913.
2002. VOISIN, B. Nouvel aperçu sur la physiologie du foie et les usages de la bile. *Gendrin, Trans. méd.*, 12:161-204, 293-359, 1833.
2003. VORT, C. Über die Beziehungen der Gallenabsonderung zum Gesamtstoffwechsel im thierischen Organismus. *Ztschr. f. Biol.*, 30: 523-61, 1894.
2004. VON BERGMANN, G. Ikterus. *Jahresk. f. ärztl. Fortbild.*, 14:No. 3, 1-9, 1923.
2005. VON BERGMANN, G. Zur Funktionellen Pathologie der Leber insbesondere der Alkohol-ätiologie der Cirrhose. *Klin. Wchnschr.*, 6:776, 1927.
2006. VON BEZNÁK, A. Der Einfluss der Galle auf die Resorption des Calciums. *Arch. f. d. ges. Physiol.*, 228:604-13, 1931.
2007. VON CZYHLARZ, E.; FUCHS, A.; and FÜRTH, O. Über die analytische Zusammensetzung der menschlichen Galle. *Biochem. Ztschr.*, 49: 120-29, 1913.
2008. VON DUSCH, T. Untersuchungen und Experimente; also Beiträge zur Pathogenese des Icterus, *u.s.w.* Habilitationsschrift. Leipzig, 1854.
2009. VON EULER, H., and KLUSMANN, E. Zur Biochemie der Carotinoide und des Vitamins C (Ascorbinsäure). *Ztschr. f. physiol. Chem.*, 219: 215-23, 1933.

2010. VON FENYVESSY, B. [Über die haematolytische Wirkung der Gallensäuren und ihrer Salze.] Hungarian. M. Orv. Arch., Budapest, 8:283-286, 1907. Biochem. Ztschr., 5:114-17, 1907.
2011. VON FÜRTH, O., and SCHOLL, R. Über den Einfluss von Gallensäuren Salzen auf Diffusions- und Resorptionsvorgänge. Biochem. Ztschr., 222:430-56, 1930.
2012. VON FÜRTH, O., and SCHÜTZ, J. Über den Einfluss der Galle auf die fett- und eisweiszspaltenden Fermente des Pankreas. Beitr. z. chem. Phys. u. Path., 9:28, 1907.
2013. VON GORUP-BESANEZ, E. F. Mikroskopische Charaktere des Menschengalle. Arch. f. phys. u. path. Chem. u. Micros., 3:1-10, 1846.
2014. VON GORUP-BESANEZ, E. F. Untersuchungen über Galle. Erlangen, 1846.
2015. VON GORUP-BESANEZ, E. F. Ein Beitrag zur Kenntniss der Zusammensetzung thierische Flüssigkeiten. Prag. Vrtljschr. f. prakt. Pharmakol., 3:82-90, 1851.
2016. VON GORUP-BESANEZ, E. F. Chemie der Galle. Lehrbuch der physiologischen Chemie, 4:509-29, Braunschweig, 1878.
2017. VONK, H. J.; ROELOFSEN, P. A.; and ROMIJN, C. Der Einfluss von Galle bei der Trypsinverdauung in vitro. Ztschr. f. physiol. Chem., 218:33-51, 1933.
2018. VON KRUSENSTERN, V. Zur Frage über das Cholestearin. Virchows Arch. f. path. Anat., 65:410-18, 1875.
2019. VON RECKLINGHAUSEN, F. D. Untersuchungen über Richitis und Osteomalazie. 2 vols. Jena: G. Fischer, 1910.
2020. VORSCHÜTZ, JOHANNES and JOSEPH. Die Bedeutung der Hämoglutination und Bakterienagglutination als Diagnostikum und ihre Erklärung. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 34:662-77, 1922.
2021. VORSCHÜTZ, J. Verschiedene Hämagglutinationsbilder bei Ikterusfaellen und ihre Bedeutung. Arch. f. exper. Path. u. Pharmakol., 95:235-37, 1922.
2022. VOSSIUS, A. Über quantitative spektralanalytische Bestimmungen des Bilirubins in der Galle. Inaug. Diss. Giessen, 1879.
2023. VOSSIUS, A. Bestimmungen des Gallenfarbstoffs in der Galle. Diss. Giessen, 1879. Arch. f. exper. Path. u. Pharmakol., 11:427-54, 1879.
2024. VOTTERO, G. Bile nera e colecistoatonia. Riforma med., 49:331-34, 1933.
2025. VULPIAN. Cours sur la bile. Recueilli par PAULIER. Paris, 1874.
2026. VULPIAN. Leçons sur l'action physiologique des substances toxiques et médicamenteuses. Paris, 1881.
2027. WAECHTER. Über das Vorkommen von Bilirubinausscheidung in Kristallform bei Icterus Gravis. Arch. path. Anat. Berlin, 190:533-35, 1907.

2028. WAGNER, F. Über den Stand der Frage der galligen Peritonitis. *Deutsche Ztschr. f. Chir.*, 168:116-32, 1922.
2029. WAGNER, R. Handwörterbuch der Physiologie. Mit Rücksicht auf physiologische Pathologie, 3:826-42, 1846.
2030. WAHLGREN, V. Über eine neue gepaarte Rindergallensäure. *Upsala, läkaref. förh.*, 7:510-27, 1901-2.
2031. WAHLGREN, V. Über Glycocholeinsäure. *Ztschr. f. physiol. Chem.*, 36:556-67, 1902.
2032. WAKABAYASHI, E. Über die Farbstoffausscheidung bei experimenteller Leberstörung. *Jap. J. Gastroenterol.*, 5:201-35, 1933.
2033. WAKEFIELD, E. G., and POWELSON, H. P. The use of dehydrocholeic acid (decholin) as a cholagogue. *Proc. Staff Meet. Mayo Clinic*, 4:49-50, 1929.
2034. WAKEFIELD, E. G.; POWELSON, H. P.; and McVICAR, C. S. The use of sodium salt of dehydrocholic acid (decholin) as a cholaretic. *Ann. Int. Med.*, 3:572-77, 1929.
2035. WALKER, E. The alleged presence of bile salts in normal blood. *Biochem. J.*, 24:1489-92, 1930.
2036. WALLACE, S. A., and SPIRO, A. Traumatic rupture of the hepatic duct. *Brit. J. Surg.*, 13:582-85, 1925-26.
2037. WALTERS, W. Preoperative preparation of patients with obstructive jaundice. *Surg. Gynec. Obst.*, 33:651-56, 1921.
2038. WALTERS, W. Preoperative preparation of patients with obstructive jaundice. *Minnesota Med.*, 6:25-28, 1923.
2039. WALTERS, W. Physiologic considerations in the treatment of obstructive jaundice. *J.A.M.A.*, 87:2153-56, 1926.
2040. WALTERS, W. Results of operations in patients with obstructive jaundice. *Proc. Staff Meet. Mayo Clinic*, 3:181-82, 1928.
2041. WALTERS, W. Obstructive jaundice: physiologic and surgical aspects. Monograph. Owatonna, Minnesota: Journal-Chronicle, 1931. Pp. 130.
2042. WALTERS, W., and BOLLMAN, J. L. Results of the accumulations of bile around the liver: clinical and experimental observations. *J.A.M.A.*, 91:239-42, 1928.
2043. WALTERS, W., and BOWLER, J. P. Preoperative preparation of patients with obstructive jaundice. *Surg. Gynec. Obst.*, 39:200-206, 1924.
2044. WALTERS, W., and DEHNE, E. A. Jaundice caused by pancreatic lesions. *Arch. Surg.*, 54:832-35, 1932.
2045. WALTERS, W.; GREENE, C. H.; and FREDRICKSON, C. H. The composition of the bile following the relief of biliary obstruction: report of a series of illustrative cases. *Ann. Surg.*, 91:686-93, 1930.

2046. WALTERS, W., and McVICAR, C. S. Relief of obstructive jaundice from tumors in the head of the pancreas. *Ann. Surg.*, **89**:237-46, 1929.
2047. WALTERS, W., and PARHAM, D. Renal and hepatic insufficiency in obstructive jaundice. *Surg. Gynec. Obst.*, **36**:605-9, 1922.
2048. WALZEL, P., and WELTMANN, O. Studien zur Gallensekretion bei einer Leber-Gallenfistel nach vorausgegangener Totalexstirpation einer sog. idiopathischen Choledochuscyste. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, **37**:437-63, 1924.
2049. WANGENSTEEN, O. H. The significance of the escape of sterile bile into the peritoneal cavity. *Ann. Surg.*, **84**:691-702, 1926.
2050. WANGENSTEEN, O. H. The haemorrhagic diathesis of obstructive jaundice and its treatment. *Ann. Surg.*, **88**:845-65, 1928.
2051. WANGENSTEEN, O. H. How long may man live with obstructive jaundice? *J.A.M.A.*, **90**:1683-87, 1928.
2052. WANGENSTEEN, O. H. Complete external biliary fistula. *J.A.M.A.*, **93**:1199-1204, 1929.
2053. WANGENSTEEN, O. H.; LEVEN, N. L.; and MANSON, M. H. Acute pancreatitis: an experimental and clinical study with special reference to the significance of the biliary tract factor. *Arch. Surg.*, **22**:47-73, 1931.
2054. WASBUTZKY, J. Über Resorption durch die Lungen. *Diss. Königsberg*, 1879.
2055. WATANABE, K. Die Glykogenbildung im Leber und Muskel durch Gallensäure und Adenylsäure. *Biochem. Ztschr.*, **255**:155-59, 1932.
2056. WATANABE, K. Bedeutung der Gallensäure im Kohlenhydratstoffwechsel. *Biochem. Ztschr.*, **274**:268-73, 1934.
2057. WATANABE, K. Die Glykogenie der Leber unter Einfluss von Adenylsäure, Cholsäure und sekundärem Phosphat. *J. Biochem.*, **21**:197-201, 1935.
2058. WATANABE, K. Einfluss der Gallensäure auf die Phosphorylierung der Adenylsäure (Adenylpyrophosphorsäurebildung) in der Leber und im Muskel. *J. Biochem.*, **21**:203-9, 1935.
2059. WATANABE, K. Über die Gallensäure der Mugilgalle. *J. Biochem.*, **22**:119-21, 1935.
2060. WATSON, C. J. Über Stercobilin, Kopromesobiliviolin und Kopronigrin. *Ztschr. f. physiol. Chem.*, **208**:101-19, 1932.
2061. WATSON, C. J. The formation and fate of derivatives of bilirubin. *J.A.M.A.*, **104**:247, 1935.
2062. WEDEKIND, A. J. *De vulnere hepatis curato*. Jena: lit. Mullerianis, 1735.
2063. WEDEL, G. W. *De bile ejusque morbis*. Jena, 1689.

2064. WEIDEMANN, H. Experimentelle Untersuchungen zur Lehre der Verdauung und Resorption verschiedener Nahrungsprodukte bei anormalem Gallenzufluss in den Verdauungsapparat. *Beitr. z. klin. Chir.*, 89:594-98, 1904.
2065. WEINBERG, M., and LEVENSON, S. Rôle de la bile dans l'étiologie et l'évolution de la péritonite biliaire expérimentale. *Compt. rend. Soc. de biol.*, 118:1302-4, 1935.
2066. WEINBERGER, E. Über das Bilifuscin. *Ztschr. f. physiol. Chem.*, 238:124-28, 1936.
2067. WEINTRAUD, W. Krankheiten der Leber. Von Noordens Handbuch der Pathologie des Stoffwechsels, 1:74-78, 1905, 1893.
2068. WEINTRAUD, W. Über die Ursache der Pulsverlangsamung beim Ikterus. *Arch. f. exper. Path. u. Pharmakol.*, 34:37-44, 1894.
2069. *WEINTRAUD, W. Gastrointestinale Autointoxikation. *Ergebn. d. allg. Path. u. path. Anat.*, 4:1-49, 1897.
2070. WEIR, J. F., and PARTCH, W. F. The relation of pain to jaundice. *Ann. Int. Med.*, 4:1509-20, 1931.
2071. WEISS, A. Ce que devient de la bile dans le canal digestif. *Centralbl. f. d. med. Wissensch.*, 23:121, 1885.
2072. WEISS, S. An evaluation of the efficacy of oleic acid with bile salts in enterohepatic disease. *J. Lab. & Clin. Med.*, 18:1016-22, 1933.
2073. WEISS, S. Diseases of the liver, gall bladder, ducts, and pancreas. New York: Paul B. Hoeber, 1935. Pp. 1000.
2074. WERNER, R. Einwirkung der Galle und gallensäuren Salze auf die Nieren. *Arch. f. exper. Path. u. Pharmakol.*, 24:31-64, 1888.
2075. WERTHEIMER, E. Expériences montrant que le foie rejette la bile introduite dans le sang. *Arch. de physiol. norm. et path.*, 3:724-34, 1891.
2076. WERTHEIMER, E. Sur la circulation entéro-hépatique de la bile. *Arch. de physiol. norm. et path.*, 4:577, 1892.
2077. WERTHEIMER, E. Sur l'élimination par le foie de la matière colorante verte des végétaux. *Arch. de physiol. norm. et path.*, 5:122-30, 1893.
2078. WERTHEIMER, E., and LEPAGE, L. Sur les voies de résorption de la bile dans le foie. *Compt. rend. Soc. de biol.*, 3:950, 1896.
2079. WERTHEIMER, E., and MEYER, E. De l'apparition de l'oxyhémoglobine dans la bile. *Arch. de physiol. norm. et path.*, 1st ser., 5:438-48, 1889.
2080. WESTPHAL, K. Die Pathologie der Bewegungsvorgänge der extrahepatischen Gallenwege. *Handbuch der normalen und pathologischen Physiologie*, 3:505-19, 1927.
2081. WESTPHAL, K., and GLEICHMANN, F. Experimentelle Erzeugung von Bilirubinkongrementen durch Stauung. *Ztschr. f. klin. Med.*, 115:329-71, 1931.

2082. WHERRY, W. B., and TASHIRO, S. Eczema, an expression of hepatic insufficiency, and its cure with bile salts. *Med. Bull. Univ. Cincinnati*, 6:156-57, 1931.
2083. WHIPPLE, A. O. Sidetracking operations for bile duct obstruction. *Ann. Surg.*, 86:540, 1927.
2084. WHIPPLE, G. H. Pigment metabolism and regeneration of hemoglobin in the blood. *Harvey Lectures*, 17:95-121, 1921-22.
2085. WHIPPLE, G. H. Origin and significance of constituents of the bile. *Physiol. Rev.*, 2:440-59, 1922.
2086. WHIPPLE, G. H. Bile salt metabolism. *J. Biol. Chem.*, 59:623, 1924.
2087. WHIPPLE, G. H., and COOK, J. V. Metabolism of dogs with sterile abscess, pancreatitis, and pleuritis. *J. Exper. Med.*, 28:223-41, 1918.
2088. WHIPPLE, G. H., and GOODPASTURE, E. W. Acute hemorrhagic pancreatitis. *Surg. Gynec. Obst.*, 17:541, 1913.
2089. WHIPPLE, G. H., and HOOPER, C. W. Hematogenous and obstructive icterus. *J. Exper. Med.*, 17:593-611, 1913.
2090. WHIPPLE, G. H., and HOOPER, C. W. Icterus. *J. Exper. Med.*, 17:612-35, 1913.
2091. WHIPPLE, G. H., and HOOPER, C. W. Bile pigment output and blood feeding. *Am. J. Physiol.*, 42:256-63, 1917.
2092. WHIPPLE, G. H., and HOOPER, C. W. Bile pigment output influenced by the Eck fistula. *Am. J. Physiol.*, 42:544-57, 1917.
2093. WHIPPLE, G. H., and HOOPER, C. W. Bile pigment metabolism. *Am. J. Physiol.*, 43:258-97, 1917.
2094. WHIPPLE, G. H., and KING, J. H. The pathogenesis of icterus. *J. Exper. Med.*, 13:115-35, 1911.
2095. WHIPPLE, G. H., and SMITH, H. P. Bile salt metabolism. *J. Biol. Chem.*, 80:685-95, 1928.
2096. WHIPPLE, G. H., and SMITH, H. P. How much bile salt circulates in the body. *J. Biol. Chem.*, 80:697, 1928.
2097. WHIPPLE, G. H., and SMITH, H. P. Bile salt metabolism: proline, tryptophane, and glycine in diet. *J. Biol. Chem.*, 89:705-17, 1930.
2098. WHIPPLE, G. H., and SMITH, H. P. Bile salt metabolism: liver injury and liver stimulation. *J. Biol. Chem.*, 89:727-38, 1930.
2099. WHITE, W. *Essay on the diseases of the bilis*. London, 1772.
2100. WIDAL, F. La Fragilité globulaire chez certains ictériques congénitaux. *Gaz. des hôp.*, 70:1275-76, 1907.
2101. WIDAL, F. Les Ictères hémolytiques acquis. *Cong. français de méd.*, 12:232-65, 1911.
2102. WIDAL, F., and ABRAMI, P. Les ictères. In *Nouveau traité de médecine*, p. 206. Masson, 1928.

2103. WIDAL, F.; ABRAMI, P.; and BRULÉ, M. Hémolyse par fragilité globulaire et hémolyse par action plasmatique. *Compt. rend. Soc. de biol.*, 63:346-49, 1907.
2104. WIEGAND, F. A. Diuretic action of intravenous sodium dehydrocholate. *J.A.M.A.*, 105:2034, 1935.
2105. WIELAND, HEINRICH. Die Synthese der Glykodesoxycholsäure und der Taurodesoxycholsäure. *Ztschr. f. physiol. Chem.*, 106:181, 1919.
2106. WIELAND, HEINRICH. Über die Synthese der Gallensäuren. *Ztschr. f. physiol. Chem.*, 167, 70-75, 1927.
2107. WIELAND, HEINRICH. Die Chemie der Gallensäuren. Nobel Prize Lecture. *Ztschr. f. ang. Chem.*, 42:421-24, 1929.
2108. WIELAND, H., and KISHI, S. Untersuchungen über die Konstitution der Gallensäuren. Über zwei neue Säuren aus Rindergalle. *Ztschr. f. physiol. Chem.*, 214:47-58, 1933.
2109. WIELAND, H., and SORGE, H. Zur Kenntnis der Choleinsäure. *Ztschr. f. physiol. Chem.*, 97:1-27, 1916.
2110. WIELAND, HERMANN. Die Desoxycholsäure und die Choleinsäuren. *Arch. f. exper. Path. u. Pharmacol.*, 86:79-92, 1920.
2111. WIELAND, HERMANN. Die Entgiftung der Desoxycholsäure durch Serum. *Arch. f. exper. Path. u. Pharmacol.*, 86:92-103, 1920.
2112. WIELAND, HERMANN. Entgiftung durch absorptive Verdrängung. Ein Beitrag zur Kenntnis der Ermüdung des überlebenden Froschherzen und der Herzwirkung des Kampfers. *Arch. f. exper. Path. u. Pharmacol.*, 89:46-65, 1921.
2113. WIELAND, HERMANN, and HILDENBRAND, T. Die Wirkung der Choleinsäure auf das Froschherz. *Arch. f. exper. Path. u. Pharmacol.*, 85:199-213, 1919.
2114. *WILBUR, R. L., and ADDIS, T. Urobilin: its clinical significance. *Trans. of the Assoc. of Am. Physicians*, 1913.
2115. WILBUR, R. L., and ADDIS, T. Urobilin: its clinical significance. *Arch. Int. Med.*, 13:235, 1914.
2116. WILDEGANS, H. Experimentelle und klinische Untersuchungen bei Cholämie. *Arch. f. klin. Chir.*, 142:698-722 and 174-76 (disc.), 1926.
2117. WILENSKY, A. O. The present status of biliary tract lesions. *M. J. & Record*, 137:191-96, 1933.
2118. WILKIE, A. L. The bacteriology of cholecystitis: a clinical and experimental study. *Brit. J. Surg.*, 15:450-65, 1927-28.
2119. WILKIE, A. L., and DOUBILET, H. Passage of cholesterol through the mucosa of the gallbladder. *Arch. Surg.*, 26:110-21, 1933.
2120. WILLIAMS, J. W. Effect of human blood serum on the toxicity of bile salts. *Proc. Soc. Exper. Biol. & Med.*, 29:916-17, 1932.

2121. WILLIAMS, J. W. Effect of human blood serum on bile salt hemolysis. *Proc. Soc. Exper. Biol. & Med.*, **29**:918-19, 1932.
2122. WILLIAMSON, A. C. Placental iron and its relationship to icterus neonatorum. *Surg. Gynec. Obst.* **37**:57, 1923.
2123. WILLOUGHBY, W. C. *The soul of bantu*. New York: Doubleday, Doran & Co., Inc., 1928.
2124. WILLSTÄTTER, R.; WALDSCHMIDT-LEITZ, E.; and MEMMEN, F. Bestimmung der pankreatischen Fettspaltung. *Ztschr. f. physiol. Chem.*, **125**:93-131, 1923.
2125. WINDAUS, A. Über die Entgiftung der Saponine durch Cholesterin. *Berl. chem. Ges.*, **42**:238, 1909.
2126. WINDAUS, A.; LÜTTRINGHAUS, A.; and DEPPE, M. Über das kristallisierte Vitamin D. (Liebigs) *Ann. d. Chem.*, **489**:252-69, 1931.
2127. WINDAUS, A., and VON SCHOOR, A. Über die Bestandteile der Hühnergalle. *Ztschr. f. physiol. Chem.*, **161**:143-46, 1926.
2128. WINDAUS, H. Experimentelle und klinische Untersuchungen bei Cholämie. *Deutsche med. Wchnschr.*, **52**:939, 1926.
2129. WINDLE, J. D. The heart's action in jaundice. *Brit. Med. J.*, **1**: 123-24, 1916.
2130. WINKELSTEIN, A. Experimentelle Untersuchungen über die Ausscheidung körperfremder Farbstoffe durch die Galle bei normalen und pathologischen Zuständen des Lebergewebes. *Arch. f. Verdauungsk.*, **32**:7, 1923.
2131. WINKELSTEIN, A., and ASCHNER, P. W. Experimental studies on color of bile from gallbladder and liver. *Am. J. M. Sc.*, **169**:842, 1925.
2132. WINKENWERDER, W. L. A study of resorption from the biliary tract, with special reference to the morphology and permeability of the cystic epithelium. *Bull. Johns Hopkins Hosp.*, **46**:272-95, 1930.
2133. WINOGRADOW, A. P. Die Wirkung von Arzneisubstanzen auf die Absonderung der Galle. *Arch. f. exper. Path. u. Pharmakol.*, **126**: 17-30, 1927.
2134. WINTELER, L. Experimentelle Beiträge zur Frage des Kreislaufes der Galle. Inaug. Diss. Dorpat: K. A. Hermann, 1892. Pp. 59.
2135. WINTER, J. Observations relatives à la recherche de l'urobiline dans la bile. *Compt. rend. Soc. de biol.*, **41**:139, 1889.
2136. WINTERNITZ, M.; DEUTSCH, J.; and BRÜLL, Z. Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektions. *Med. Klin.*, **27**:986-88, 1931.
2137. WINTERNITZ, M.; DEUTSCH, J.; and BRÜLL, Z. Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion. *Med. Klin.*, **28**:831-32, 1932.

2138. WISNER, F. P., and WHIPPLE, G. H. Variations in the output of bile salts and pigments during 24-hour periods, observations on standard bile fistula dogs. *Am. J. Physiol.*, **60**:119-33, 1922.
2139. WIT, H. Die physikalische Entfärbbarkeit von Galle. *Biochem. Ztschr.*, **207**:141-45, 1929.
2140. WOHLGEMUTH, J. Über die Bildungsstätte des Fibrinogens. Ein Beitrag zur Frage der Beziehungen zwischen Pankreas und Leber. *Berl. klin. Wchnschr.*, **54**:87-90, 1917.
2141. WOHLGEMUTH, J. Die Leber als sekretorisches Organ. In Oppenheims Handb. d. Biochem. d. Menschen u. d. Tiere, 4. Jena: Gustav Fischer, 1924. Pp. 603.
2142. WOLFER, J. A. Acute pancreatitis. *Internat. Surg. Dig.*, **7**:211-21, 1929.
2143. WOLFER, J. A. Bile leakage from the cystic duct following cholecystectomy: experimental study of obliteration of cystic duct stump. *Surg. Gynec. Obst.*, **49**:462-72, 1929.
2144. WOLFER, J. A. The role of the pancreatic juice in the production of gallbladder disease. *Surg. Gynec. Obst.*, **53**:433-47, 1931.
2145. WOLFER, J. A. Pancreatic juice as a factor in the etiology of gallbladder disease. *Proc. Chi. Soc. Int. Med.*, **9**:85-86, 1932.
2146. WOLFF, H. J. Physiologic action of toluylendiamin and its relation to experimental jaundice. *Proc. Staff Meet. Mayo Clinic*, **8**:697-99, 1933.
2147. WRIGHT, A., and WHIPPLE, G. H. Bile cholesterol. Fluctuations due to diet factors, bile salt, liver injury and hemolysis. *J. Exper. Med.*, **59**:411-25, 1934.
2148. WUNDERLICH, C. A. Zur intoxicationsartigen Form des perniziösen Icterus. *Arch. d. Heilk.*, **4**:145-60, 1863.
2149. WURTZ, C. A. Historie chimique de la bile à l'état sain et à l'état pathologique. Strassbourg, 1839.
2150. WYSS, O. Beitrag zur Histologie der icterischen Leber. *Virchows Arch. f. path. Anat.*, **35**:553-60, 1866.
2151. YANO, Y. Beitrag zum Studium der Farbstoffausscheidung durch Leber und Niere. *Jap. J. Gastroenterol.*, **5**:123-27, 1933.
2152. YAMASAKI, K. Beiträge zur Kenntnis der Hammarstenschens Reaktion der Cholsäure. *J. Biochem.*, **18**:311-22, 1933.
2153. YAMASAKI, K. Vorkommen der Taurocholsäure in der Hühnergalle. *J. Biochem.*, **18**:323-24, 1933.
2154. YAMASAKI, K. Über einige Choleinsäuren. *J. Biochem.*, **22**:243-49, 1935.
2155. YAMASAKI, K. Isomerisation der Apocholsäure und der Dioxycholsäure. *Ztschr. f. physiol. Chem.*, **233**:10-12, 1935.

2156. YAMASAKI, K., and KYOGOKU, K. Über das Schicksal der Dehydrocholsäure und Dehydrodesoxycholsäure im Krötenorganismus. *Ztschr. f. physiol. Chem.*, 233:29-35, 1935.
2157. YAKOSHEVSKI, S. [Pathologo-anatomical changes in some animal organs under the poisonous influence of biliary acid salts.] Russian. St. Petersburg, 1882.
2158. YEO, G. F., and HERROUN, E. F. A note on the composition of human bile obtained from a fistula. *J. Physiol.*, 5:116-23, 1884.
2159. YLPPÖ, A. Icterus neonatorum und Gallenfarbstoffsekretion beim Foetus und Neugeborenen. *Ztschr. f. Kinderh.*, 9:208, 1913.
2160. YLPPÖ, A. Zwei Fälle von kongenitalem Gallengangsverschluss. *Ztschr. f. Kinderh.*, 9:319-33, 1913.
2161. YONEMURA, S. Über die Gallodesoxycholsäure aus Hühnergalle und ihren Einfluss auf die Pankreassteapsinwirkung. *J. Biochem.*, 6:287-96, 1926.
2162. YONEMURA, S. Über die Gallensäurebildung. *J. Biochem.*, 7:101-16, 1927.
2163. YONEMURA, S., and FUJIHARA, M. Über die Beziehungen zwischen Gallensäure, Schlangengift und Cholesterin. *J. Biochem.*, 6:91-100, 1926.
2164. YOSHIMURI, S. Über das Allantoin in der Galle des Hundes. *J. Biochem.*, 10:435-42, 1929.
2165. YOUNG, A. W. The movements of the isolated small intestine and the action of various drugs and extracts upon them. *Quart. J. Exper. Physiol.*, 8:347, 1915.
2166. YUROVSKI, D. [Gas interchange and heat production under the influence of poisoning by biliary acid salts.] Russian. St. Petersburg, 1888.
2167. ZAMARONI, V., and GUASSARDO, G. Paratiroidi calcemia. Eliminazione biliare del Ca. *Pathologica*, 22:341-48, 1930.
2168. ZANETTI, C. U. Sulla non prevalenza dei sali potassici nella bile dei pesci marini. *Roma, rend. acc. lincci*, 11:275-77, 1902.
2169. ZERI, A. Viscosità della bile umana. *Arch. di farmacol. sper.*, 4:279-88, 1905.
2170. ZIEGLER, A. M., and ORR, T. G. Chemical changes in the blood of the dog in experimental bile peritonitis. *J. Exper. Med.*, 53:865-68, 1931.
2171. ZIEGLER, E. E. The specific effect of bile salts on pneumococci, and on pneumococcus pneumonia. *Arch. Int. Med.*, 46:644-56, 1930.
2172. ZIEGLER, E. E. Sodium dehydrocholate: its specific effect on pneumococci. *J. Lab. & Clin. Med.*, 16:3-8, 1931.

2173. ZIN, A. Die erythropoietische Wirkung des Bilirubins und Häoglobins bei hungernden und milchanämischen Tieren. Ztschr. f. d. ges. exper. Med., 99:664-69, 1936.
2174. ZILLOCCI, E. Ricerche sulla secrezione della bile nel drenaggio delle vie biliari. Arch. ital. di chir., 39:301-59, 1935.
2175. ZONDEK, S. G. Zur Frage der Vagus- und Sympathikus-Wirkung. Arch. f. exper. Path. u. Pharmakol., 143:192-208, 1929.
2176. ZUMBUSCH, L. R. Über das Bilifuscin. Ztschr. f. physiol. Chem., 31:446-59, 1901.
2177. ZUMBUSCH, L. R. Notiz über die Galle von Isabellbären. Ztschr. f. physiol. Chem., 35:426-31, 1902.
-

INDEX

INDEX

- Abdominal muscles in bile peritonitis, 216-17, 218
- Abdominal operations and bile output, 23
- Abilirubinemia, 75
- Abortion, 178, 179
- Abscess
 - aseptic, 224
 - atheromatous, 96, 100
 - due to subcutaneous injection of bile, 13, 123
 - local, in jaundice, 237
 - metastatic, 220
- Acetylcholine, 44
- Acholia, 12, 42, 60, 237, 242, 245, 246
- Acidity
 - of bile, 25
 - gastric
 - and jaundice, 183
 - and ulcers, 191, 192
- Acidosis and external biliary fistula, 16, 265-66
- Acute pancreatitis, 204-7
- Acute yellow atrophy, 246
- Adhesions, 222
- Adrenalin
 - and bile, 43
 - and pH of bile, 25
 - and sugar in bile, 30
- Aerobes, 221
- Air, introduction of, into vein, 8
- Albumin
 - in gallbladder, 58
 - in urine, 113, 165, 168, 172, 176, 216, 217, 218
- Albuminocholia, 27
- Albuminuria, 15, 115, 171, 177, 233, 247
- Alcohol, 43
- Alcoholism, chronic, 104
- Alkali reserve and biliary fistula, 262, 265-66
- Alkalinity of bile; *see* pH of bile
- Amino acids, 29, 248, 257, 268
- Amylase, 28
- Anaerobes, 198, 221
- Aniline, 33
- Anemia, 115
 - and bile in the blood, 114, 116
 - and bile-pigment output, 50
 - and biliary fistula, 115, 262, 263, 264
 - of brain, 10
 - in jaundice, 10, 112, 115
 - and lecithin output, 52
 - and ligature of common bile duct, 115
 - pernicious, bilirubin in, 76
- Animal charcoal; *see* Charcoal
- Animals
 - action of bile acids on, 70, 71
 - experiments on, history of, 7-17
 - pigments in, 75
 - relative toxicity of bile from different, 15, 19
- Anterior pituitary, 43
- Anthrodesoxycholic acid, 67
- Anticholagogues, 23, 44
- Antiseptic properties of bile, 196, 198, 201, 202
- Anuria, 217, 218, 236
- Apocholeic acid, 66-67
- Apocholeic acid, 269
- Apoplexy, 3
- Appetite, loss of
 - and feeding of bile, 182
 - in obstructive jaundice, 255
- Arcus senilis, 96
- Arsenic, 21, 26
- Arsphenamine poisoning, 278
- Arthritic pain, 144, 278
- Ascites, 174, 256
- Aseptic abscess, 224
- Aseptic bile, 245

- Ataxia, 233
- Atheromatous abscesses, 96, 100
- Atophan and pH of bile, 25
- Atropine, 23, 43, 44, 98
and heart, 150, 151, 152, 153, 154, 158
- Autointoxication, 161
- Autolytic protein metabolism, bile salts
and, 68
- Bacteria
and bile, 39, 46, 59, 102, 195, 196-203,
220, 221
and bile acids, 210
and bile salts, 197, 199, 200, 221
in biliary peritonitis, 210, 214, 215,
217, 218, 220-21, 224
and dehydrocholic acid, 271
and formation of bilirubin, 49
in gallbladder, 197-98, 200, 201, 202
with gallstones, 197
and icterus, 243-44, 245
and pH of bile, 25
and sodium dehydrocholate, 199, 271
toxicity of, 221
- Balloon method for testing intestinal
activity, 181, 184, 185, 186, 190
- Beneficial action of bile, 192, 194, 195;
see also Detoxifying agent, bile as
- Bicarbonate in gallbladder, 58
- Bile (*see also* Whole bile)
characteristics of, 22-26
complexity of, 6, 20-22
composition of, 26-32
early terminology, 1-2
peritoneal fluid called "bile," 219
present definition of term, 6
toxicity of, 1-8, 10-19, 40, 62, 79, 81,
103, 139, 173, 208-9, 210, 220,
223, 233, 236, 246, 255, 260-61,
269, 279-81
- Bile absence and toxicity, 262, 268
- Bile acids, 5, 20 f., 60 n.; *see also* Bile
salts
and amino acids, 268
and animals, 70, 71
and bacteria, 196, 197, 198, 210
and bile output, 174, 269, 270, 272-74
and bile peritonitis, 224
and bile pigment, 8, 9, 168
and blood, 60, 106, 112, 113, 224, 234,
269
and bile pigments, change to, 9
in biliary obstruction, 231
and bleeding, 124, 127-28, 129, 134
in common-duct obstruction, 109-10
concentration of bile acid, 108-10
in jaundice, 109, 173, 233, 235
in obstructive jaundice, 109, 110
and blood capillaries, 224
and blood pressure, 157, 272
and bone metabolism, 268
and calcium metabolism, 267
and carotin, 267
and cholemia, 150
and cholesterol, 97
colorless, 9
concentration of, 210
daily output of, 44
death due to, 11, 253
decomposition of, by blood, 8
dehydro-forms of, 66
diuretic action of, 176
early work on, 5 f.
fate of, 52-55
in feces, 8, 167
feeding of, 46
in gallbladder bile, 57, 58
and gastric ulcer, 68
and heart, 10, 148, 150, 155, 156, 224,
269
in intestinal tract, 8, 188-89
intracardiac injection of, 10
intravenous injection of, 9, 10, 189,
269
and jaundice, 109, 173, 231, 233, 235
and kidneys, 8, 224
and ligation of arteries, 11
and liver, 8, 16, 168, 233
and nervous system, 138, 141
in obstructive jaundice, 55, 109-10,
112, 231
optical properties of, 25
origin of, 44-48
output of; *see* Bile acids, daily output
of
and pancreatic juice, 67
and peptic ulcers, 192
and phosphatase, 268
pK of, 26
and placenta, 179
and plants, 70, 71

- and production of lecithin, 52
- purity of, 61
- and putrefaction, 196, 197
- rotary dispersion of, 25
- and secondary surgical shock, 224
- and secretions, salivary and nasal, 189
- and skeletal muscle, 161
- surface tensions of, and toxicity, 16
- taurin, 69-71; *see also* Taurin
- tests for, 108, 109, 111, 167, 169
- and their salts, 60-69; *see also* Bile salts
- therapeutic effects of, 269-78
- and tissues, 224, 269
- toxicity of, 10, 16, 60-72, 89, 97, 114, 224, 269, 270
- and urine, 8, 113, 167, 168, 170, 174, 189, 234
- and uterus, 178
- and vitamins, 267
- Bile-calcium relativity constant, 42
- Bile constituents, 20-40
 - action of, on heart, 146-49, 150
 - black bile, 105; *see also* Black bile
 - cerebrin, 101-2
 - cholesterol, 94-101; *see also* Cholesterol
 - early work on, 5 f.
 - green bile, 105
 - intravenous injections of, 11
 - lecithin, 101; *see also* Lecithin
 - mucin, 102; *see also* Mucin
 - origin of, 42, 166
 - pleiochromic bile, 105
 - pseudo-mucin, 102; *see also* Pseudo-mucin
 - removal of, by liver, 18, 42
 - rust bile, 105
 - toxicity of, 94-105
 - variations in, 102-3
 - white bile, 103-4; *see also* White bile
- Bile ducts (*see also* Common bile duct)
 - and concentration of bile, 57
 - congenital atresia of, 252-54
 - dilatation of, 257
 - ligation of, 9, 254
 - obstruction of, 9, 231
 - and jaundice, 255; *see also* Obstructive jaundice
- Bile flow and ligatures, 9
- Bile loss (external biliary fistula) and length of life, 262-68; *see also* Life, length of
- Bile mucus, 5, 192
- Bile peritonitis, 210-24; *see also* Peritonitis, local
 - with perforation, 211-23
 - clinical, 211-12
 - discussion on, 219-23
 - experimental, 212-18
 - treatment, 223
 - without perforation, 210-11
 - death due to, 211 ff., 216 ff., 221, 223 f.
- Bile pigments, 28, 32-33, 240, 241
 - and bile acids, 8, 9, 168
 - in biliary fistula, 264
 - bilifuscin, 91; *see also* Bilifuscin
 - bilihumin, 91; *see also* Bilihumin
 - biliprasin, 91; *see also* Biliprasin
 - bilirubin, 73-90; *see also* Bilirubin
 - biliverdin, 91; *see also* Biliverdin
 - in blood, 170, 171, 225-26
 - and blood pigment, 9
 - and chloroform, 247
 - and coloring; *see* Color; Coloring
 - ~matter of bile
 - in common-duct obstruction, 256
 - in congenital atresia of bile ducts, 252
 - and contusion, 73; *see also* Contusions
 - crystals of, 9, 91
 - in dissociated biliary retention, 228
 - in extravasated blood, 73, 76, 226
 - fate of, 55-57
 - and heart, 148, 153
 - from hematin, 8
 - and hemoglobin, 55, 73
 - in icterus neonatorum, 250, 251
 - in intestinal tract, 55, 188
 - and jaundice, 176, 225, 226, 227, 234, 235-36
 - and kidneys, 173
 - and ligation of arteries, 11
 - and ligation of common duct, 165, 167
 - in liver, 16
 - in mucous membrane in jaundice, 236
 - and nervous system, 138
 - nontoxicity of, 73-93
 - origin of, 8, 9, 48-51, 168
 - in plasma in jaundice, 235-36
 - in saliva, 55

- Bile Pigments—continued**
 in sclerotic membrane in jaundice, 236
 in sweat, 55; *see also* Perspiration
 in tears, 55
 tests for, 108
 in tissues, 56
 toxicity of, 10, 12, 73-93, 246, 279, 281
 in urine, 8, 9, 54, 55, 112-13, 165, 166-67, 168, 169, 170, 171, 218, 235-36
 urobilin, 91-93; *see also* Urobilin
 various forms of, 91
- Bile retention (icterus), 225-48; *see also* Jaundice; Icterus**
- Bile salts, 28, 60-69; *see also* Bile acids**
 absorption of, from intestine, 110
 and acholia, 12
 action of animal charcoal on, 12
 and albuminuria, 15, 115
 and autolytic protein metabolism, 68
 and bacteria, 197, 199, 200, 221
 and bleeding, 15, 115, 125 ff.
 in blood, 15, 106, 108, 109, 110, 111, 113, 114, 115, 116-18, 121, 122, 125 ff., 170, 171, 176, 231, 233
 and blood clots, 11
 and blood coagulation, 63, 68, 80
 and blood pressure, 157
 and blood serum, 118
 and blood sugar, 110
 and calcium-phosphorus balance, 268
 and central nervous system, 19
 and cholemia, 12
 as choleric, 269
 and cholesterol, 51, 209
 and collodion ultrafilters, 68
 in common-duct obstruction, 256-57
 concentration of, 60, 208, 210
 and congenital atresia of bile ducts, 252, 253
 conjugated, 60, 72
 cytotoxic effect of, 15
 daily output of, 27, 60
 death due to, 12, 62, 63, 65, 68, 189, 213, 214
 and disruption of spermatozoa, 15, 115
 and egg albumin, 68
 enterohepatic circulation of, 57
 excretion of, variability of, 21-22
 feeding of, 25, 85
 and output of, 46-47
 and output of cholesterol, 51
 filtered, specific gravity and toxicity of, 79
 and fluid secretion, 219
 and gallbladder, 66
 in gallbladder bile, 60
 and heart, 19, 147-49, 151, 153, 154, 158-59
 in hepatic insufficiency, 247
 and human serum, 68
 and intestinal tract, 23, 110, 185, 186, 187, 188, 189, 190
 intracarotid injection of, 157
 intrajugular injection of, 157
 intraperitoneal injection of, 157
 intravenous injection of, 9, 11, 157, 167, 176, 223, 245
 in jaundice, 231, 233
 and kidneys, 12, 173
 and lecithin, 209
 and liver, 42, 47, 48, 53, 60, 245
 and lysis of protozoa, 15, 115
 by mouth, and pH of bile, 25
 and nervous system, 137 ff.
 and nuclein-splitting, 68
 and obstructive jaundice, 47, 52
 origin of, 44-45, 47, 48
 output of, 46-47; *see also* Bile salts, daily output of
 and oxygen consumption of tissues, 68-69
 and peptic ulcers, 192, 193
 and placenta, 179
 and pneumonia, 199
 and pregnancy, 59, 251
 and protective substances in blood, 116-18
 and proteins, 15, 117, 118, 209
 rectal injection of, 189
 and red blood cells, 11, 15, 62, 64, 65-67
 and respiration, 19
 and skeletal muscle, 160, 162, 163
 subdural injection of, 139
 tests for, 108, 109, 111, 140, 169, 279, 280
 and thrombosis, 11, 128
 and tissues, 68-69, 80
 toxicity of, 8, 10, 11, 12, 60-69, 89, 115, 116-18, 121, 122, 138, 144, 233, 246, 279, 280, 281

- and tracheal mucosa, 19
- and uremia, 12
- in urine, 167, 169-70, 171, 176, 177, 251
- and uterus, 178, 179
- and white blood cells, 15
- Bile thrombi; *see* Thrombosis
- Biliary diabetes, 76; *see also* Diabetes
- Biliary fistula; *see* External biliary fistula
- Biliary fistula bile (*see also* Fistula bile)
 - color of, 22
 - daily output of, 23
- Biliary humors, 4
- Biliary peritonitis, 210; *see also* Bile peritonitis
- Biliary tract, anomaly of, 254
- Bilicyanin, 32
- Bilifuscin, 32, 91
- Bilihumin, 32, 91
 - in urine, 166
- Biliprasin, 32, 91
- Bilipurpurin, 32
- Bilirubin, 6, 32, 55, 73-90, 121, 241
 - absorption of
 - from intestine, 50, 85
 - by lymphatics, 85
 - by portal vein, 85
 - in bile, 56, 74, 77, 115
 - in blood, 56, 74, 83, 120, 121, 226, 234, 270
 - concentration of, 83, 107-8, 227-28
 - during pregnancy, 251
 - and blood pressure, 86, 87
 - in blood serum, 73-74, 75, 76
 - in cachexia, 76
 - in cirrhosis of the liver, 76
 - color of, 22
 - in common-duct obstruction, 256, 257
 - concentration of, 208
 - and congenital atresia of bile ducts, 253
 - and conjunctiva-coloring, 78
 - and constipation, 78
 - and convulsions, 86
 - crystals of, 73, 74, 139, 227
 - daily output of, 32, 74, 92
 - death due to, 13, 79, 80
 - detoxification of, 89-90
 - and dyspneic breathing, 86
 - in egg tract of birds, 74
 - and erythrocytes, 56, 73, 121
 - fate of, 56
 - feeding of, 84-85
 - in gallbladder, 58
 - in gallbladder bile, 57, 58
 - and heart, 86-87, 146-47
 - and hemoglobin, 73
 - in hemolytic icterus, 76
 - in icterus neonatorum, 249, 250, 251
 - and intestine, 50, 56-57, 85
 - intralymphatic injection of, 85-86
 - intravenous injection of, 77, 81-82, 83, 86-87, 167
 - and isolated heart, 86-87
 - and itching, 238, 239
 - in jaundice, 56, 76, 90, 107, 227, 229, 233, 235
 - in kidney, 76
 - in kidney disease, 76, 171, 227
 - and liver, 42, 48, 76
 - and nervous system, 86, 139
 - in obstetrical trauma, 76, 251
 - and obstipation, 86
 - in obstructive jaundice, 56, 107, 229
 - origin of, 9, 48-51
 - output of; *see* Bilirubin, daily output of
 - in pathological conditions, 55, 76
 - in pernicious anemia, 76
 - in perspiration, 74
 - in pneumonia, 76
 - in pregnancy, 76, 178, 251
 - and pulse rate, 86, 87
 - purity of, 78
 - and salivation, 86
 - and skin-coloring, 76
 - solubility of, 79
 - in spinal fluid, 56
 - subcutaneous injection of, 83-84
 - as test of liver function, 82-83, 90
 - tests for, 88-89, 107, 108, 229, 279
 - and thrombosis, 13
 - and tissues, 76, 79-80, 83
 - toxicity of, 13, 14, 61, 62, 64, 71, 78, 79, 81-82, 86, 89, 90, 279
 - in tuberculosis, 76
 - in urine, 56, 74, 76, 77, 78, 92, 166, 167, 170, 174, 227-28, 234

- Bilirubinemia**, 75, 228
 and contusions, 76, 251
 in extrauterine pregnancies, 76, 251
 and extravasated blood, 251
 and fracture, 76, 251
 in new-born infants, 76, 250, 251
 and obstetric trauma, 251
 in obstructive jaundice, 76
 and operations, 251
 pathological, 75-77
- Bilirubinuria**, 77, 228
- Biliverdin**, 32, 55, 75, 91, 229
 color of, 22
 hematopoietic activity of, 121
 in urine, 166
- Birds** (*see also* Eggs)
 bilirubin in egg tract of, 74
 coloring of droppings and egg shells of, and bile pigments, 91
- Black bile**, 3, 4, 22, 105, 137
- Black jaundice**, 80, 246
- Bleeding**
 in acute pancreatitis, 204, 207
 and bile in blood, 124 ff., 134
 and bile acids, 124, 127-28, 129, 134
 in bile peritonitis, 213, 216, 217, 218, 223
 and bile salts, 15, 115, 125 ff.
 and biliary fistula, 262, 264
 and calcium, 131, 135, 136
 and cholesterol, 135
 and common-duct obstruction, 124 ff., 136
 in congenital atresia of bile ducts, 253, 254
 extravasations in tissues, 73, 76, 226, 251
 and galactose, 135
 and glucose, 131, 135, 136
 and glycerol, 135
 in jaundice, 124-36, 233, 235, 236, 238, 254
 and calcium, 130-31, 135, 136
 and coagulation, 124, 125, 126 ff., 134-36
 death due to, 124-25, 127, 128, 248
 and disturbed liver function, 132-34, 136
 and fibrinogen, 129-30, 133-34, 136
 occurrence, 124-26
 and peptic ulcers, 191, 193
 and platelets, 131-32
 and prothrombin, 132, 135, 136
 treatment of, 134-36
 in obstructive jaundice, 124 ff., 136
 and peptic ulcers, 191, 192, 193, 194
 and phosphorus, 136
 and sodium glycocholate, 127
 and sodium taurocholate, 127, 135
 spontaneous, and biliary fistula, 262
 and surgical risk in jaundice, 259, 260, 261
 and whole-blood transfusion, 135
- Blood** (*see also* Blood cells; Blood serum; Erythrocytes; Leukocytes; Red blood cells; White blood cells)
 bile in, 80
 and bleeding, 124 ff., 134
 concentration of, 106-11
 and death, 113
 and fistula output of bile, 11
 and hemoglobin, 114, 115, 116, 117
 bile acids in; *see* Bile acids, and blood
 bile pigment in, 170, 171, 225-26
 bile salts in, 15, 106, 108 ff., 113 ff., 121 f., 125 ff., 170 f., 176, 231, 233
 and bleeding, 15, 115, 125 ff.
 in jaundice, 231, 233
 in biliary fistula, 262, 264
 bilirubin in, 56, 74, 83, 120, 121, 234, 270
 concentration of, 83, 107-8, 227-28
 formation of, 48
 during pregnancy, 251
 cholesterol in, 51, 95, 96, 97, 99, 114, 121, 270-71
 coagulation of; *see* Coagulation of blood
 in congenital atresia of bile ducts, 252
 decomposition of bile acids by, 8
 and dehydrocholic acid, 270-71
 detoxification of, 177
 in dissociated jaundice, 110-11
 extravasated; *see* Extravasations of blood
 fibrinogen in; *see* Fibrinogen
 in icterus neonatorum, 251
 ion concentration of, and bile, 143
 lecithin in, 116-17, 121
 and liver destruction, 8, 172
 nonprotein nitrogen in, 260

- osmotic pressure of, 41
- protective substances in, preventing hemolysis by bile salts, 116-18
- removal of bile constituents from, 18, 42
- and sodium dehydrocholate, 270-71
- and sodium desoxycholate, 270
- and sodium glycocholate, 113, 114, 115, 117, 127, 270
- and sodium taurocholate, 15, 114, 115, 117, 121, 127
- taurin in, 69, 113
- in urine, 171, 172, 216, 223
- urobilin in, 50, 92, 93
- Blood capillaries; *see* Capillaries
- Blood cells, effect of bile on, 112-23; *see also* Erythrocytes; Leukocytes; Red blood cells; White blood cells
- Blood clots due to bile salts, 11; *see also* Embolism; Thrombosis
- Blood fats, 114; *see also* Fats
- Blood flow and ligatures, 9
- Blood pigment, 9, 240
- Blood plasma in jaundice, 235-36
- Blood pressure
 - and bile, 151, 156-58
 - and bile acids, 157, 272
 - in bile peritonitis, 218, 222, 223
 - and bile salts, 157
 - and bilirubin, 86, 87
 - in hepatic insufficiency, 247
 - and jaundice, 158, 232, 236
 - and sodium cholate, 87, 157
 - and sodium dehydrocholate, 158
 - and sodium glycocholate, 87, 157
 - and sodium taurocholate, 157
 - and variation in bile, 41
- Blood salts, 110, 111
- Blood serum (*see also* Blood)
 - and bile salts, 68, 118
 - bilirubin in, 73-74, 75, 76
 - cholesterol in, 95, 96
 - coloring of, 74, 75
 - in jaundice, 236
 - and desoxycholate, 155
- Blood sugar, 110, 245, 257
- Blood transfusion, 260
- Blood urea, 172-73, 235
- Blood vessels and intravenous injections
 - of bile and bile salts, 126
- Boiling of bile, and toxicity, 14, 79
- Bone metabolism, 262, 265-68
- Bowel movements, 78, 191
- Bradycardia, 139, 145, 148 ff., 156, 158 f., 215, 217 f., 233 ff.
- Brain (*see also* Central nervous system; Nerves; Nervous system)
 - anemia of, in jaundice, 10
 - and bile, 139-41
 - cholesterol in, 94, 96
- Cachexia
 - in common-duct obstruction, 256
 - due to carcinoma, 76
 - of inanition, 76
 - and peptic ulcers, 193, 194
- Caesarean section, 59
- Calcium
 - and bile, 89-90, 223, 260-61, 262
 - and coagulation of blood, 130-31, 135, 136, 260
 - in gallbladder, 58, 59
 - and heart, 149, 159
- Calcium bilirubinate, 89, 147
- Calcium metabolism, 16, 253
- and biliary fistula, 262, 265-66, 267-68
- Calculi, 254
- Canalization, spontaneous, 255, 258
- Cancer, 143, 159, 259
- Capillaries (blood)
 - and bile acids, 224
 - bleeding from, 125
 - mechanical blocking of, 8
 - thrombi in; *see* Thrombosis
- Carcinoma, 76, 259; *see also* Cancer
- Carotid artery, injection into; *see* Intra-carotid injection
- Carotin, 33, 74, 75, 240, 267
- Carotinoids, 74, 240
- Caseous tuberculous lesions, 96
- Casts in urine, 171, 172, 177
- Catalepsy, 137
- Catarrhal jaundice, 234, 238
- Cecostomy, 185

- Central nervous system (*see also* Brain; Nerves; Nervous system)
 and bile, 143, 152
 and bile salts, 19
 and bilirubin, 86
- Cerebral edema, 246
- Cerebral emboli, 138
- Cerebrin, 101-2
- Charcoal, animal, 12, 79, 81, 88, 175
- Chemistry
 of bile, 5 f., 7, 25-32
 of bile constituents, 20, 21
- Chenocholate, 162
- Chenodesoxycholic acid, 67
- Chloride in gallbladder, 57, 58, 59
- Chloroform and bile, 26, 43, 247
 and bile pigment, 247
 and bile salts, 47
 and cholesterol output, 51, 247
- Chloroform anesthesia, bile in, 21, 247
- Chloroform poisoning, 42, 104, 230, 232, 244
- Chlorophyll, 75
- Cholagogues, 23, 44, 45, 269, 278
- Cholangitis, 104, 230
- Cholecystenterostomy, 254, 258
- Cholecystitis, 58, 197, 205
- Cholecystogastrostomy, 191
- Cholecystotomy, 263
- Choledochogastrostomy, 182
- Choleic acid
 fate of, 54-55
 toxicity of, 64, 67
- Choleic acid enteroliths, 67
- Cholelithiasis and biliary fistula, 262
- Cholemia, 12, 150, 174, 211, 213, 233, 235, 245
- Cholemic hepatitis, 247
- Cholemic nephritis, 173; *see also* Nephritis
- Choleprasin, 32
- Cholera, 22
- Choleretics, 44, 269 ff., 278
- Cholerrhagia, 247
- Cholesteatomata, 96
- Cholesterin, 58, 99
- Cholesterol, 6, 20, 28, 57, 94-101, 220, 223
 abnormal locations of, 96-97
 absorption of, by intestine, 51
 action of, 97
 activated, and osteoporosis, 265
 and bile, 95, 96, 97, 114
 and bile acids, 97
 in blood, 51, 95, 96, 97, 99, 114, 121, 270-71
 in blood serum, 95, 96
 in brain, 94, 96
 and chloroform, 51, 247
 and coagulation of blood, 135
 in common-duct obstruction, 256-57
 and cytolytic activity of bile salts, 209
 daily output of, 51, 94
 death due to, 99, 100
 in eggs, 94
 and emboli, 11, 99, 100, 149
 in gallbladder, 57, 58, 59
 and gallstones, 96, 100
 in glands, 94
 and heart, 148, 149
 and infections, 96
 in intestinal tract, 51, 188
 intravenous action of, 11, 98-100
 and jaundice, 96, 235, 240
 in kidney, 94
 and ligation of common duct, 97
 and liver, 42, 94, 97, 101
 in nerves, 94, 96
 normal location of, 94-96
 in obstructive jaundice, 97, 256
 origin of, 51-52
 output of, and bile salts, 51
 and peptic ulcers, 193
 protective role of, 97-98
 and red blood cells, 96, 97
 solubility of, 94
 subcutaneous injection of, 100
 test for, 95
 in tissues, 94, 96
 toxicity of, 10, 11, 96, 98, 99, 100, 101
 and toxicity of bile acids, 97
 in urine, 95, 97
 in white blood cells, 95
 and xanthoma, 240
- Cholesterolemia, 97, 100

- Cholesteryl oleate, 192, 193
- Cholic acid, 25, 33, 36, 106
 - and assimilation of sugar, 46
 - and bone metabolism, 268
 - fate of, 52, 54
 - and heart, 147, 154-55
 - origin of, 17, 44
 - and putrefaction, 197
 - and rickets, 29, 267
 - and skeletal muscle, 163
 - test for, 21, 106
 - toxicity of, 54, 64, 65, 67, 69, 70, 71, 275
- Cholehematin, 32, 50
- Choline and heart, 153, 159
- Choloidinic acid, 64, 70, 162
- Choluria, 233
- Chromolipoid, 74, 75
- Chronic acholuric jaundice, 120
- Chronic suffering and bile, 3
- Chyle, 255
- Chyme, 255
- Cinchophen, 144
- Cirrhosis of the liver
 - bile in, 21
 - and bile acids in urine, 168
 - bilirubin in, 76
 - in common-duct obstruction, 256
 - and green bile, 105
- Cisternal injection of bile, 140
- Climate and variation in bile, 21
- Coagulation of blood
 - and bile salts, 63, 68, 80
 - and calcium, 130-31, 135, 136, 260
 - and cholesterol, 135
 - in congenital atresia of bile ducts, 253
 - and phosphorus, 136
 - and prothrombin, 132, 135, 136
 - and sodium glycocholate, 127
 - and sodium taurocholate, 127, 135
 - and surgical risk in jaundice, 259-60, 261
 - and transfusion, 260
- Colloid ultrafilters and bile salts, 68
- Colloidal osmotic pressure of bile, 25-26
- Colon, 188-91; *see also* Intestine
- Coloring matter of bile, 2-3, 12, 22
- Colorless biliary acids, 9
- Coma, 15, 138, 140, 213, 216, 218, 233, 236, 237
- Common bile duct (*see also* Bile ducts)
 - ligation of, 18, 193, 231, 243, 255-56
 - and recanalization, 258
 - obstruction of, 42, 228, 237; *see also* Jaundice, obstructive
 - and bile acids in blood, 109-10
 - and bile pigment, 256
 - and bile salts, 256-57
 - bilirubin in, 256, 257
 - and cholesterol, 256-57
 - complete, 258-59
 - and heart, 256
 - and hemorrhage, 124 ff., 136
 - and itching, 238
 - and jaundice; *see* Jaundice, obstructive
 - and length of life, 258-59
 - and liver, 242-43, 256, 257, 258
 - and mucin in bile, 27
 - and peptic ulcers, 191, 192, 194
 - and phosphatase, 268
 - occlusion of, 257, 259
- Complexity of bile, 6, 20-22
- Composition of bile, 26-32
- Concentration of bile, 22-23, 57, 208, 210
 - in blood, 106-11
- Conception, jaundice and, 179
- Congenital atresia of bile ducts, 252-54
- Congenital hemolytic icterus, 232
- Congenital obstructive jaundice, 249
- Conjugated bile salts, 60, 72
- Conjugated cholates, 111
- Conjugated glycuronic acids, 28
- Conjugation and toxicity of bile acids, 72
- Conjunctivae, 78, 225, 236, 249, 252, 255
- Constipation, 78, 191
- Constituents of bile; *see* Bile constituents
- Contusions, 73, 76, 251
- Convulsions, 3, 11, 15, 16, 86, 137, 138-39, 140, 237
- Copraporphyrin, 33

- Creatinine, 29, 142
 Crystallized bile, death due to, 11
 Curare, 98
 Cytolytic activity of bile salts, 209
 Cytotoxic effect of bile salts, 15
- Death (*see also* Life, length of)
 from acute pancreatitis, 204, 205
 and changes in bile, 29
 due to
 air being introduced into vein, 8
 bile in blood, 113
 bile acids, 11, 253
 bile peritonitis, 211 ff., 216 ff., 221, 223 f.
 bile salts, 12, 62, 63, 65, 68, 189, 213, 214
 bilirubin, 13, 79, 80
 bleeding in jaundice, 124-25, 127, 128, 248
 cholesterol, 99, 100
 common-duct occlusion, 257
 congenital atresia of bile ducts, 253-54
 crystallized bile, 11
 decolorized bile, 81
 feeding of bile, 182, 183
 glycocholic acid, 214
 hepatic insufficiency, 248
 injection of bile, 137, 140
 injection of filtered ox bile, 10
 injection of fistula bile, 81
 intravenous injection of bile, 7
 mechanical blocking of capillaries, 8
 peptic ulcers, 193
 Platner's crystallized bile, 11
 sodium taurocholate, 11
 subcutaneous injection of bile, 12 f.
 taurin, 69
 taurocholic acid, 214
 uremia in jaundice, 248
 following cerebral emboli, 138
 and white bile, 103, 104
- Debility in jaundice, 236
- Decholin, 51; *see also* Dehydrocholic acid
- Decolorization of bile, 88
- Decolorized bile, 8, 12, 13, 79, 81; *see also* Filtered bile
- Decolorized fistula bile, 13 f., 81
- Decomposition of bile, 39; *see also* Stagnant bile; Standing, changes in bile on
- Dehydration, 222-23
- Dehydroapocholic acid, 66-67
- Dehydroapocholic acid, 67
- Dehydrobilirubin, 49
- Dehydrocholic acid, 67, 148, 186, 269-78
 and bacteria, 271
 and blood, 270-71
 and heart, 271-72
 and kidneys, 275
 and liver, 274-75
 and output of bile, 272-74
 and respiration, 272
 toxicity of, 270 ff.
- Dehydrodesoxycholic acid, 269
- Delirium, 137, 235, 236
- Density of bile, 14
- Depressing substance in bile, 14 f.
- Depression in jaundice, 144
- Derangement of general sensations in jaundice, 236
- Desoxycholate and heart, 148, 155-56
- Desoxycholic acid, 25, 72
 as choleric, 269
 and rickets, 29
 and skeletal muscle, 163
 toxicity of, 64, 65, 68, 270, 275
- Destructive action of bile on erythrocytes, 112-16
- Detoxification
 bile as agent of, 201-2; *see also* Protective action of bile
 of bilirubin, 89-90
 of blood, 177
 of heart muscle, 155-56
- Diabetes, 96
 biliary, 76
 pancreatic, 29, 46
- Diarrhea, 180, 182, 188, 189-90, 191, 201, 215, 216, 217, 218, 236
- Diathermy, 43
- Diet
 and biliary fistula, 263
 and obstructive jaundice, 259
 and pigmentation of blood, 226
 and variation in bile, 21, 23, 25, 29-30, 41, 45, 237

- Digestion, 236, 269; *see also* Fats, absorption of; Malnutrition
- Digitalis, 154
- Diseases
and bile, 21, 36-37, 237
early idea of, 3 ff., 237
and liver, 281
- Dissociated biliary retention, 228
- Dissociated jaundice; *see* Jaundice, dissociated
- Dissociation constant of bile acids, 26
- Diuretic action of sodium dehydrocholate, 176, 275
- Double Thiry-Vella fistula, 185
- Drugs, 22, 26, 37-38
- Duodenal fistula, 187
- Duodenal injection of bile, 184
- Duodenal-tube bile, 67
- Duodenal ulcers, 192, 193, 262; *see also* Peptic ulcers
- Duodenum, 184, 186, 188, 189, 194
- Dyes, 22, 38, 102, 105
- Dyscholia, 242
- Dyspnea, 86, 139
- Eclampsia, 179
- Edema, 174, 176, 204, 214, 217, 218, 237, 246
- Egg albumin and bile salts, 68
- Eggs, cholesterol in, 94; *see also* Birds
- Emboli (*see also* Thrombosis)
and bile, 18, 80, 128, 157, 194
cerebral, 138
and cholesterol, 11, 99, 100, 149
mucous, 138
- "Emotional icterus," 230
- Enterobiliary fistula, 268
- Enterohepatic circulation, 11, 57
- Enterostomy, 185
- Enzymes, 28
- Epinephrine; *see* Adrenalin
- Ergosterin, 29, 43
- Ergotamine, 43, 44
- Erysipelas and urobilin, 92
- Erythrocytes (*see also* Blood; Red blood cells)
and bile, 112-22
and bilirubin, 56, 73, 121
and destructive action of bile, 112-16
fragility of, 119-21
in hematogenous icterus, 250, 251
and inhibitory action of sugars on hemolysis, 121
in obstructive jaundice, 117, 119, 120
and protective substances in blood, 116-19
sedimentation, 121
solution of, 122
- Essential hemorrhagic jaundice of Monneret, 246
- Estrogen, 179
- Ether, 43
- Ethereal sulphates, 28
- Excitation, 15
- Exercise and variation in bile, 21, 41
- Exhaustion in jaundice, 236
- Experimental history of bile, 7-1
- External biliary fistula
and acidosis, 16, 265-66
and alkali reserve, 262, 265-66
and anemia, 115, 262, 263, 264
and bile pigment, 264
and bile quantity, 10 f.
and blood, 262, 264
and bone abnormalities, 262, 265-68
and calcium metabolism, 262, 265-66, 267-68
and caoutchouc bag, use of, 264
and cholelithiasis, 262
and diet, 263
and duodenal ulcers, 262
and erythrocytes, 264
experimental work with, 21, 23
and feeding of bile, 262, 263, 266
and hemoglobin, 264
and infection, 262
and intestinal disturbance, 262
and length of life, 262-68
and leukocytes, 264
and loss of weight, 262, 263
and osteoporosis, 262, 265-68
and parathyroids, 262, 265

- External biliary fistula—*continued*
 and peptic ulcers, 191, 192, 194
 and phosphates, 262, 266
 and phosphorus metabolism, 266,
 267-68
 and spleen, 264
 and spontaneous fractures, 262, 265
 and urine, 266
- External pancreatic fistula and peptic
 ulcers, 191
- Extrahepatic obstruction and jaundice,
 252-61
- Extrauterine pregnancies, 76, 251
- Extravasations of blood in tissues, 73,
 76, 226, 251
- Exudates
 coloring of, in jaundice, 236
 effect of, on action of bile, 18
- Eyelids, 240
- Eyes, color of, in jaundice, 225, 226, 227,
 236
- Eyesight in jaundice, 236
- Fasting
 and bile output, 180
 and bile-salt production, 46
 and white bile, 104
- Fasting icterus, 230
- Fatality; *see* Death
- Fate of bile, 41, 52-59
 in jaundice, 234
 in obstructive jaundice, 256
- Fats, 159
 absorption of
 and bile, 196-97
 and bone metabolism, 266, 267
 in jaundice, 236, 253
 in bile, 26, 28
 in blood, 114
 and cytolytic activity of bile salts, 209
 in obstructive jaundice, 256
- Feces
 bile in, 180, 188
 bile acids in, 8, 167
 bile pigments in, 55
 in congenital atresia of bile ducts,
 252-53
 glyccocoll in, 71
 in icterus neonatorum, 251
- in jaundice, 236
 in obstructive jaundice, 196
 stercorin in, 96
 taurin in, 69
 urobilin in, 93
 urobilinogen in, 92, 93
- Feeding (*see also* Mouth)
 of bile, 262, 263, 266
 death due to, 182, 183
 of bile and liver, 268
- Fermentation, 196
- Fever, 43, 235
- Feverless icterus, 145
- Fibrinogen
 in jaundice, 129-30, 133-34, 136, 233
 and liver damage, 133-34
 normal content of blood, 133-34
- Filtered bile (*see also* Decolorized bile)
 death due to, 10
 effect of injection of, 8, 137, 138
 and nervous system, 137
 toxicity of, 12, 13, 61, 79, 138
- Fistula bile (*see also* Biliary fistula bile)
 bile-salt concentration of, 60
 daily output of, 237
 death due to, 81
 decolorized, 13 f., 81
 density and toxicity of, 14
 lecithin in, 101
 after ligation of portal vein, 14
 specific gravity of, 24, 81
 toxicity of, 13 f., 62, 81
- Fistulas, intestinal, types of, 185
- Fluid (*see also* Secretions)
 called "bile," 219
 peritoneal, and secondary surgical
 shock, 222-23, 224
 pathological, bile pigment in, 56
- Fractures
 and bilirubinemia, 76, 251
 spontaneous, and biliary fistula, 262,
 265
- Freezing-point of bile, 24
- Galactose and coagulation of blood, 135
- Gallbladder
 albumin in, 58
 bacteria in, 197-98, 200, 201, 202
 and bile salts, 66

- bilirubin in, 58
 - calcium in, 58, 59
 - changes of bile in, 57-59
 - chloride in, 57, 58, 59
 - cholesterol in, 57, 58, 59
 - congenital absence of, 254
 - disease of, and jaundice, 58
 - and lecithin, 57
 - necrosis of, and bile, 208-9
 - and obstructive jaundice, 256
 - phosphorus in, 58, 59
 - pressure within, and heart rate, 159
 - protein in, 58
 - pseudo-mucin in, 102
 - sodium in, 57
 - sodium chloride in, 58
- Gallbladder bile
 - bacteria in, 197-98
 - bile acids in, 57, 58
 - bile salts in, 60
 - bilirubin in, 57, 58
 - color of, 22
 - constituents of, 29
 - density and toxicity of, 14
 - lecithin in, 101
 - mucin in, 102, 209
 - specific gravity of, 24
 - stagnant, toxicity of, 14
 - toxicity of, 14, 62, 67
 - whole
 - filtered, 79
 - and heart, 87
 - and pulse rate, 87
- Gallbladder fistula, 115, 187
- Gallodesoxycholic acid, 67
- Gallosterin, 267
- Gallstones, 20, 32, 58, 230, 257
 - and acute pancreatitis, 204
 - bacteria with, 197
 - and black bile, 105
 - and cholesterol, 96, 100
 - and pregnancy, 251
- Gastric acidity
 - jaundice and, 183
 - ulcers and, 191, 192
- Gastric hemorrhages, 191, 192, 193, 194
- Gastric motility of the hunger type, 183
- Gastric mucosa; *see* Mucosa
- Gastric secretion, 183
- Gastric ulcers, 68, 191-94
- Gastrobiliary fistula, 268
- Gastrointestinal system
 - action of bile on, 180-95
 - colon, 188-91
 - intestinal obstruction, 194-95; *see also* Intestinal obstruction
 - peptic ulcers, 191-94
 - small intestine, 183-88; *see also* Intestine; Small intestine
 - stomach, 10, 12, 182-83, 192
 - disturbances of, in jaundice, 236
 - and ligation of common duct, 184, 193
- Gastrojejunostomy, 193
- Gestation, 96
- Giddiness in jaundice, 236
- Glands, cholesterol in, 94
- Glucose and coagulation of blood, 131, 135, 136
- Glycemia, 29, 142
- Glycerol, 135, 193
- Glycerophosphoric acid, 268
- Glycocholia, 29
- Glycocholic acid, 25, 60, 72
 - death due to, 214
 - dissociation constant of, 26
 - in jaundice, 234
 - pK of, 26
 - toxicity of, 64
- Glycocol, 67, 71
 - in feces, 71
 - and heart, 71, 148
 - and nervous system, 142
 - putrefaction and, 197
 - toxicity of, 8, 10, 70, 71
 - and urea, 71
 - in urine, 71
- Glycogen, 142, 166, 233, 245, 248, 260
- Glycosuria, 46
- Glycuronic acids, conjugated, 28
- Golgi apparatus, 41
- Grave essential jaundice of Beneuvre, 246
- Green bile, 105
- Green jaundice, 80

- Headache in jaundice, 236
- Heart
 and bile, 7, 10, 11, 18, 145-56, 158-59
 and bile acids, 10, 148, 150, 155, 156, 224, 269
 and bile pigment, 148, 153
 and bile salts, 19, 147-49, 151, 153, 154, 158-59
 and bilirubin, 86-87, 146-47
 and calcium, 149, 159
 and cholesterol, 148, 149
 and cholic acid, 147, 154-55
 and choline, 153, 159
 and dehydrocholate, 148
 and dehydrocholic acid, 271-72
 and desoxycholate, 148, 155-56
 and glycocoll, 71, 148
 isolated, and bilirubin, 86-87
 and jaundice, 145, 149, 152, 153, 156, 158, 159, 235, 236
 and liver disturbance, 149-50, 159
 and nerves, 150-53
 and potassium, 149
 and sodium cholate, 87
 and sodium dehydrocholate, 271-72
 and sodium desoxycholate, 271
 and sodium glycocholate, 87, 147, 148, 152, 271
 and sodium taurocholate, 152
 and taurin, 148
 and taurocholic acid, 147
 weakness of, in common-duct obstruction, 256
 and whole gallbladder bile, 87
- Heartbeat in bile peritonitis, 218; *see also* Pulse
- Heart muscle, 101, 146, 152, 153-56
- Heart rate (*see also* Pulse)
 in congenital atresia of bile ducts, 253
 and pressure within gallbladder, 159
- Hematin, 8, 9
- Hematogenous icterus, 113, 249, 250, 251
- Hematoidin, 226
- Hematoporphyrin, 33, 239
- Hematuria, 168, 177
- Hemins, 49
- Hemoglobin, 75, 77, 241
 and bile in blood, 114, 115, 116, 117
 and bile pigments, 55, 73
 and biliary fistula, 264
 and bilirubin, 73
- Hemoglobinocholia, 32
- Hemoglobinuria, 16, 113, 118
- Hemolytic disease, 230
- Hemolytic jaundice, 76, 120, 145, 229, 238, 252
- Hemolytic sera, 118
- Hemorrhage; *see* Bleeding
- Heparin, 86
- Hepatectomy, 47, 49, 246, 247
- Hepatic disorders; *see* Liver
- Hepatic duct, ligation of, 254
- Hepatic-duct bile, 62
- Hepatic insufficiency, 235, 246-48, 259-60; *see also* Cholemia
- Hepatorenal disease, 174-75
- Hepatotoxins, 47
- Heteroalbuminocholia, 26
- Hiccuping in bile peritonitis, 213
- H-ion concentration of bile, 24-25; *see also* Ion concentration; pH
- Histamine, 25, 43, 44, 209
- History of bile, 1-6
 experimental, 7-17
- Hormones, 28, 43
- Horse serum, color of, 74, 75
- Human serum, color of, 74, 75; *see also* Blood serum
- Humors, early ideas regarding, 4 f.
- Hunger, 183
- Hydrobilirubin, 32, 75
- Hyochoic acid, 64, 70, 162
- Hyperamphatonia, 153
- Hyperbilirubinemia, 73, 76, 178, 226
- Hypercalcemia, 153
- Hypercholesterinemia, 121
- Hypercholesterolemia, 98, 149
- Hypercholinemia, 153
- Hyperesthesia and bile, 15
- Hyperglycemia, 46
- Hyperkinesia, 137

- Hypertrophic cirrhosis of the liver, bilirubin in, 76
- Hypervagotonia, 150 ff., 158
- Hypocalcemia, 153
- Hypocholesterolemia, 149
- Hypocholia, 60
- Hypocholinemia, 153
- Hypoglycemia, 247
- Hypophysin, 44
- Hypothyroidism, 58
- Hypotonia, 153
- Ictère total*, 176
- Icterogen poisoning, 243, 244
- Icterus, 12, 18, 104, 119, 225-48; *see also*
 - Jaundice
 - and bile acids in blood, 109
 - and bile salts in blood, 114
 - cholesterol in, 96
 - congenital hemolytic, 232
 - "emotional," 230
 - fasting, 230
 - feverless, 145
 - hematogenous, 113, 249, 250, 251
 - hemolytic, 76
 - and infections, 198
 - local, 226
 - of the new-born; *see* Icterus neonatorum
 - stasis, 243
- Icterus gravida, 251
- Icterus gravis, 10, 213
- Icterus neonatorum, 73, 75, 77, 230, 249-51, 252
- Ileum, 184
- Inanition, cachexia of, and bilirubin, 76
- Infarcts, 96, 250
- Infections
 - bile in, 21
 - and bile in peritoneum, 211, 212
 - and biliary fistula, 262
 - and cholesterol, 96
 - and icterus, 198
 - and mucin in bile, 27
- Infectious jaundice, 234
- Injections of bile
 - death due to, 137, 140
 - types of, 18
- Insulin, 25, 30, 43, 245
- Intestinal acholia and urobilin, 93
- Intestinal disturbance and biliary fistula, 262
- Intestinal hemorrhages, 194
- Intestinal obstruction
 - bacteria and, 196
 - and bile, 194-95
 - toxicity in, 201
- Intestine (*see also* Colon; Small intestine)
 - absorption of fats from, 196-97
 - bacteria in, 196, 198, 201
 - bile in, 180-81
 - and fistula output of bile, 10
 - bile acids in, 8, 188-89
 - bile pigments in, 55, 188
 - and bile salts, 23, 110, 185, 186, 187, 188, 189, 190
 - and cholesterol, 51, 188
 - fate of bilirubin in, 50, 56-57, 85
 - mucosa of; *see* Mucosa
 - serosa of; *see* Serosa
 - and urobilin, 93
- Intracardiac injection
 - of bile, 10
 - of bile acids, 10
- Intracarotid injection
 - of bile, 10, 140
 - of bile salts, 157
- Intracolonic injection of bile, 190
- Intra-intestinal injection of bile, 184
- Intrajugular injection
 - of bile salts, 157
 - of filtered bile, 137
 - of sodium glycocholate, 137, 138
 - of sodium taurocholate, 137
- Intralymphatic injection of bilirubin, 85-86
- Intraperitoneal injection
 - of bile, 18, 157, 172, 191, 193-94, 213-14, 215, 216, 218, 220, 221
 - plus calcium, 260-61
 - of bile salts, 157
 - of lecithin, 101
 - of sodium dehydrocholate, 277
 - of sodium glycocholate, 213
- Intraspinal injection of bile, 140
- Intrathoracic injection of bile, 220

- Intravenous injection**
 of bile, 7, 8, 11, 13, 18, 138, 157, 183,
 184, 185, 189, 193-94, 245
 plus calcium, 260-61
 of bile acids, 9, 10, 189, 269
 of bile constituents, 11
 of bile salts, 9, 11, 157, 167, 176, 223,
 245
 of bilirubin, 81-82, 83, 86-87, 167
 of cholesterol, 11, 98-100
 of filtered bile, 8, 138
 of lecithin, 101
 of sodium dehydrocholate, 270 ff.
 of sodium glycocholate, 8, 138, 169,
 213
 of sodium taurocholate, 8
 of urobilin, 50-51
- Ion concentration of blood, effect of bile**
 on, 143; *see also* H-ion concentra-
 tion; pH
- Iron and icterus neonatorum**, 250, 251
- Irradiated ergosterol**, 267
- Isatin**, 51
- Itching**, 236, 238-40, 247
- Jaundice**, 4, 18-19, 112, 225, 279, 280;
see also Icterus
 and absorption of fats, 236, 253
 and anemia of brain, 10
 and arthritis, 144, 278
 bile acids in blood in, 109, 173, 233,
 235
 in bile peritonitis, 218
 and bile pigment, 176, 227, 234, 235-
 36
 bile salts in blood in, 231, 233
 and bilirubin, 76, 90, 107, 227, 229,
 233, 235
 black, 80, 246
 bleeding in; *see* Bleeding, in jaundice
 and blood pressure, 158, 232, 236
 blood urea in, 235
 cancer and, 143, 159
 catarrhal, 234, 238
 causes of death in, 248
 cholesterol in, 96, 235, 240
 chronic acholuric, 120
 classification of, 227-30; *see also*
 Jaundice, three types of
 color of skin and eyes in, 225, 226,
 227, 236, 238, 251
 congenital obstructive, 249
 definition of term, 225, 226
 dissociated, 110-11, 120, 170, 234
 essential hemorrhagic, of Monneret,
 246
 etiology, 226-27
 and excretion of bile acids, 53
 extrahepatic obstructive and, 252-61
 and eyesight, 236
 fate of bile in, 234
 fate of bile acids in, 55
 feces in, 236
 feigned, 225
 fibrinogen in, 129-30, 133-34, 136, 233
 and fragility of red cells, 119-21
 and gallbladder disease, 58
 and gastric acidity, 183
 glycocholic acid in, 234
 grave essential, of Beneuvre, 246
 green, 80
 and heart, 145, 149, 152, 153, 156, 158,
 159, 235, 236
 hemolytic, 76, 120, 145, 229, 238, 252
 hepatic insufficiency and, 246-48
 infectious, 234
 intoxication of, 231 ff.
 and kidney, 172-73, 177, 233, 235,
 245, 246
 the liver in, 231, 232-33, 234, 235,
 236, 241-48
 and local peritonitis, 237
 loss of weight in, 233; *see also* Jaun-
 dice, malnutrition in; Nutritional
 disturbances in
 malignant, 137, 245, 246
 malnutrition in, 143, 159, 252, 253,
 255; *see also* Jaundice, nutritional
 disturbances in; Jaundice, loss of
 weight in
 and menstruation, 179
 mental symptoms in, 137
 nervous symptoms in, 10, 143-44
 neutral sulphur in, 234, 236
 in new-born; *see* Icterus neonatorum
 and nitrogen metabolism, 233, 234,
 236
 of nonobstructive origin, 232
 not a disease, 248
 nutritional disturbances in, 10; *see*
also Jaundice, loss of weight in;
 Jaundice, malnutrition in

- obstructive, 41, 159, 228, 229, 232, 255, 280; *see also* Common duct, obstruction of; Jaundice, extra-hepatic obstruction
- and anemia, 115
- and bile acids, 55, 109-10, 112, 231
- and bile salts, 47, 52
- bilirubin in, 56, 107, 229
- bilirubinemia in, 76
- bleeding in, 124 ff., 136
- and carotin, 267
- and cholesterol, 97, 256
- color of skin in, 256
- complete, 268
- congenital, 249
- and diet, 259
- and erythrocytes, 117, 119, 120
- experimental, 254-58
- and fate of bile, 256
- and fats, 256
- feces in, 196
- and gallbladder, 256
- lecithin in, 256
- and length of life, 258-59, 268
- and liver, 149, 243, 254, 257
- and operations, 259-61
- and peptic ulcers, 193
- sodium taurocholate in, 256
- and stomach, 183
- and taurocholate, 47
- and urine, 8, 165, 166-67, 168-69, 170, 174, 255, 256
- and urobilin, 92
- and peevishness of temper, 236
- physiologic, 225-26, 249-51
- pigmentation in, 176, 225, 226, 227, 234, 235-36
- plasma (blood) in, 235-36
- platelets in, 131-32
- in pregnancy, 179, 251
- preoperative treatment in, 260-61
- and protein in urine, 165
- and pruritus, 237, 238, 239
- purpura in, 125
- receding, 230
- renal dissociation, 176
- respiration in, 237
- and sadness, 236
- and saliva, 236
- and sedimentation rate for red blood cells, 121
- severe, of Ozanam, 246
- simple, 243, 246
- and skeletal muscle, 160-61, 162, 163
- spleen in, 236
- surgical risk in, 259-61
- sweat in, color of, 236
- symptoms of, 230-41, 245
- taste in, 236
- taurocholic acid in, 234, 236
- and temporary teeth, 251
- theories regarding, 246, 249-50
- three types of, 169-70; *see also* Jaundice, classification of
- toxic, 243
- typhoid, of Leberet, 246
- and ulcers, 193, 194
- uremia in, death due to, 248
- urine in, 165, 166, 169, 170, 171, 173-77, 226, 233, 234, 236, 237; *see also* Jaundiced urine
- and urobilin, 93
- and uterus, 179
- and xanthoma, 240
- Jaundiced urine, 139, 173-77; *see also* Jaundice, urine in
- color of, 165, 166-67
- Jejunum, 184, 185
- Jercorin, 28
- Keratin-coated bile pills, 181
- Kidney
- and bile, 166, 171-73
- and bile acid, 8, 224
- and bile pigment, 173
- and bile salts, 12, 173
- and bilirubin, 56, 76, 227
- cholesterol in, 94
- as compensatory organ, 37
- and dehydrocholic acid, 275
- and detoxification of blood, 177
- disease of, bilirubin in, 76, 227
- in icterus neonatorum, 250
- and jaundice, 172-73, 177, 233, 235, 245, 246
- and ligation of common duct, 173, 174
- and liver, 174-75, 247
- and sodium dehydrocholate, 275
- and urobilin, 92
- Koproporphyrin, 33
- Kymograph, 10

- Lactic acid, 28
- Laparotomy, 211
- Lecithin, 26, 28, 101, 220, 223
and cytolytic activity of bile salts, 209
and gallbladder, 57
and gastric ulcers, 192
intraperitoneal injection of, 101
in obstructive jaundice, 256
origin of, 52
and peptic ulcers, 193
and pregnancy, 52
and tetanus of muscle, 163
toxicity of, 101
- Leprosy, 92
- Leucine, 168
- Leukocytes, 115, 122-23, 264; *see also*
Blood; White blood cells
- Life (*see also* Death)
length of
and bile loss, 263
and external biliary fistula, 262-68
and obstruction of common duct,
258-59
and obstructive jaundice, 258-59,
268
and necessity for bile, 41, 263, 264
- Ligation
of arteries, 11
and bile ducts, 9, 254
and bile flow and blood flow, 9
of common duct, 18, 193, 231, 243,
255-56, 258
and anemia, 115
and bile pigment in urine, 165, 167
and changes in kidney, 173, 174
and cholesterol, 97
effect of, on gastrointestinal system,
184, 193
and recanalization, 255, 258
of hepatic duct, 254
and liver, 9
of portal vein, 14
of thoracic duct, 255-56
- Lipase, 268
- Lipides, 68
- Lipochrome, 74
- Lipoids, 52, 117
- Lipolytic enzymes, 28
- Lithocholic acid, 67
- Liver
and bacteria, 199-200, 245
and bile, 26 f., 32, 245, 281
and bile acids, 8, 16, 168, 233
and bile constituents, 18, 42, 166
bile pigments in, 16
and bile salts, 42, 47, 48, 53, 60, 245
and bilirubin, 42, 48, 56, 76, 82-83,
90, 92
and cholesterol, 42, 51, 94, 97, 101
cirrhosis of; *see* Cirrhosis of liver
and common-duct obstruction, 242-
43, 256, 257, 258
as compensatory organ, 37
in congenital atresia of bile ducts, 252
and dehydrocholic acid, 274-75
disease of, 5, 92, 138, 230
disturbed function of, 172
and bile, 26 f., 32
and bleeding, 132-34, 136
and fibrinogen, 133-34
and heart, 149-50, 159
and pruritus, 239
and urine, 172
and xanthoma, 240
due to alcohol, 92
effects of removal of, 8, 233
failure of, to secrete bile, 42
functions of, 242
test for, 82-83, 90
hepatic insufficiency, 246-48
in icterus neonatorum, 249, 250
in jaundice, 231, 232-33, 234, 235,
236, 241-48
and kidney, 174-75, 247
and ligatures, 9
and obstructive jaundice, 149, 243,
254, 257
and origin of bile, 46
and origin of bile constituents, 42, 166
regulation of amount of lipoids by, 52
and sodium dehydrocholate, 274
and white bile, 61, 104
- Liver bile, 208, 209
- Liver cells and bile, 122
- Local icterus, 226
- Lutein, 75
- Lymph after removal of liver, 8
- Lymphatic leukemia and urobilin, 92
- Lymphatics, 85, 256

- Lysin, 66
 Lythocholic acid, 72
- Malaria, 92, 93, 225
 Malignant jaundice, 137, 245, 246
 Malnutrition in jaundice, 143, 159, 252, 253, 255; *see also* Nutritional disturbances; Weight, loss of
 Mechanical stasis, 229
 Meconium in congenital atresia of bile ducts, 252-53
 Melancholia, 3, 137, 144
 Melancholy humors, 4
 Menstruation, jaundice and, 179
 Mental symptoms in jaundice, 137
 Mesobilirubin, 75
 Mesobiliviolin, 75
 Metabolic rate and bile, 143
 Metallic poisoning, 103
 Metallic salts in bile, 102
 Metastatic abscesses, 220
 Methods of investigation of bile, 18-19
 Methyl-ester- β -cholic acid, 267
 Migraine, 278
 Milk, coloring of, in jaundice, 236
 Mineral poisoning, 37-38
 Minerals in bile, 30-32
 Miscarriage, 178, 179
 Mouth (*see also* Feeding)
 bile given by, 7, 245
 bile salts given by, 25
 sodium dehydrocholate given by, 270, 277, 278
 Mucin, 209
 in bile, 16, 27, 28, 102, 209, 220
 in gallbladder bile, 102, 209
 in obstructive jaundice, 256
 Mucinocholia, 27
 Mucosa
 gastric, 191
 intestinal, 19, 180-81, 184, 188
 Mucous emboli, 138
 Mucous membrane, bile pigment in, in jaundice, 236
 Mucus, bile, 5, 192
 Mucus-free decolorized bile, 8
 Muscarine, 98
 Muscles
 abdominal, in bile peritonitis, 216-17, 218
 effect of bile on nerves and, 141-42, 163
 heart; *see* Heart muscle
 paralysis of, 162-63
 skeletal; *see* Skeletal muscle
- Nasal secretion and bile acids, 189
 Necrosis
 bile and, 18, 214
 of gallbladder, 208-9
 Nephritis, 76, 93, 96, 171, 172, 173
 Nephrosis, 172, 173
 Nerves (*see also* Brain; Central nervous system; Nervous system)
 and bile, 141-44, 150-53, 163
 cholesterol in, 94, 96
 and heart, 150-53
 Nervous system (*see also* Brain; Central nervous system; Nerves)
 and bile, 80, 137-44, 163
 and bilirubin, 86, 139
 and disease of liver, 138
 and glyccoll, 142
 and jaundice, 10, 143-44
- New-born infants
 bilirubin crystals in, 73
 bibilirubinemia in, 76, 250, 251
 and congenital atresia of bile ducts, 252-54
 jaundice in; *see* Icterus neonatorum
- Nitrogen metabolism (*see also* Non-protein nitrogen)
 in congenital atresia of bile ducts, 253
 in jaundice, 233, 234, 236
- Nomenclature; *see* Terminology
 Nonprotein nitrogen
 in bile, 29
 in blood, 260
Nouvelle Solution, 99
 Nuclein-splitting and bile acid, 68
 Nutritional disturbances in jaundice, 10;
 see also Malnutrition; Weight, loss of
- Obstetrical trauma, bilirubin in, 76, 251
 Obstipation and bilirubin, 86

- Obstruction
 of bile ducts; *see* Bile ducts, obstruction of
 of common bile duct; *see* Common bile duct, obstruction of
 of pancreatic duct; *see* Pancreatic duct, obstruction of
- Obstructive jaundice; *see* Jaundice, obstructive
- Odor of bile, 2
- Oestrous hormone, 28
- Olein, 28
- Oliguria, 172, 176
- Oliguric nephrosis, 173
- Oöcyanin, 75
- Open wounds; *see* Wounds
- Operations
 abdominal, and bile output, 23
 and bilirubinemia, 251
 obstructive jaundice and, 259-61
- Oral feeding; *see* Feeding; Mouth
- Origin of bile, 41-52
- Osmotic pressure
 of bile, 25-26, 41
 of blood, 41
- Osteomalacia, 266, 267, 268
- Osteoporosis, 16, 262, 265-68
- Output of bile (*see also* Quantity)
 abdominal operations and, 23
 and choleretic effect of bile acids, 174, 269, 270, 272-74; *see also* Choleretics
 daily, 22, 23, 41, 60
 and fasting, 180
 and time of day; *see* Time of day
- Ovaries, 58, 179
- Oxycholic acid, 269
- Oxygen consumption of tissues, bile salts and, 68-69
- Palmatin, 28
- Pancreatic diabetes, 29, 46
- Pancreatic duct
 and congenital atresia of bile ducts, 253
 injection of bile into, 204-5, 206
 obstruction of, 159
 and peptic ulcers, 197
- Pancreatic enzyme, 28
- Pancreatic juice
 and acute pancreatitis, 204, 205, 206-7
 and bile, 16, 195
 and bile acids, 67
 and peptic ulcers, 193
- Pancreatitis; *see* Acute pancreatitis
- Paracentesis, 211, 217
- Paralysis, 15, 137, 140
 of muscles, 162-63
- Parasympathetics, 43
- Parathyroids, 262, 265
- Pathological bile, 21, 36-39
- Pathological bilirubinemia, 75-77
- Peevishness of temper in jaundice, 236
- Peptic ulcers, 191-94; *see also* Duodenal ulcers
- Pericardium, 19
- Periodicity of bile formation; *see* Time of day
- Peritoneal fluid called "bile," 219
- Peritonitis (*see also* Bile peritonitis)
 local, in jaundice, 237
- Pernicious anemia, bilirubin in, 76
- Perspiration, bilirubin in, 74; *see also* Sweat
- Petechiae, 264
- pH of bile, 24-25, 40, 66, 199, 208-9;
see also H-ion concentration; Ion concentration
- Phenylhydrazine HCl, 33
- Phlorizin and bile, 43
- Phocataurocholic acid, 67
- Phosphates, 28, 58, 262, 266
- Phosphatase, 28, 268
- Phosphatides, 163, 193
- Phospholipins, 101, 102
- Phosphoric acid, 28
- Phosphorus
 and bile, 21, 26, 34
 and biliary fistula, 266, 267-68
 and coagulation of blood, 136
 in gallbladder, 58, 59
- Phosphorus, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000

- Physical reactions of bile, 25-26
- Physiologic jaundice, 225-26, 249-51
- Pigments; *see* Bile pigments
- Pilocarpine, 43, 44
- Pituitary body, anterior, 43
- Pituitrin, 43, 178
- pK of bile acids, 26
- Placenta
 - action of bile on, 179
 - iron contents of, and icterus neonatorum, 250
- Plantar extensor response, 235
- Plants
 - action of bile acids on, 70, 71
 - pigments in, 75
- Plasma in jaundice, 235-36
- Plasmochrome, 74
- Platelets in jaundice, 131-32
- Platner's crystallized bile, death due to, 11
- Pleiochromic bile, 105
- Pneumonia, 21, 76, 92, 93, 199, 237
- Poisonings, 21
 - arsphenamine, 278
 - chloroform, 42, 104, 230, 232, 244
 - metallic, 103
 - mineral, 37-38
 - phosphorus, 104, 230, 267
 - sulphanol, 33
- Polycholia, 60, 237, 246
- Polycythemia and urobilin, 92
- Polypeptides, 248
- Porphyrins, 33
- Portal vein
 - and bilirubin absorption, 85
 - ligature of, and toxicity of bile, 14
- Potassium, 42, 149
- Pregnancy
 - and bile salts, 59, 251
 - and bile secretion, 58
 - bilirubin in, 76, 178, 251
 - extrauterine, 76, 251
 - and gallstones, 251
 - jaundice in, 179, 251
 - and lecithin output, 52
- Premature labor, 178
- Preoperative treatment in jaundice, 260-61
- Preservative, bile as a, 8
- Prostration, 140
- Protean character of bile, 22
- Protective action of bile, 192, 194, 195; *see also* Detoxifying agent, bile as
- Protective role of cholesterol, 97-98
- Protective substances in blood preventing hemolysis by bile, 116-19
- Protein
 - in bile, 27
 - and bile salts, 15, 117, 118, 209
 - in gallbladder, 58
 - in urine, in jaundice, 165
- Protein osmotic pressure of bile, 26
- Proteolytic enzymes, 28
- Prothrombin and coagulation of blood, 132, 135, 136
- Protoporphyrin, 33
- Protozoa, lysis of, and bile salts, 15, 115
- Pruritus, 236, 237-40
- Pseudo-mucin, 102, 209
- Puerperium and bile secretion, 58
- Pulse (*see also* Heartbeat; Heart rate)
 - in bile peritonitis, 218
 - and bilirubin, 86, 87
 - in congenital atresia of bile ducts, 253
 - fast; *see* Tachycardia
 - in hepatic insufficiency, 247
 - in icterus neonatorum, 251
 - slow; *see* Bradycardia
 - and whole gallbladder bile, 87
- Purgative, bile as, 189
- Purity
 - of bile-acid products, 61
 - of bilirubin, 78
- Purpura in jaundice, 125
- Putrefaction (*see also* Decomposition)
 - and bile, 198, 201
 - and bile acids, 196, 197
 - and cholic acid, 197
 - and taurin, 197
- Quantity of bile, 22-23; *see also* Output of bile
 - in external biliary fistula, 10 f.
- Quinine, 43

- Reactions of bile
 pH, 24-25
 physical and chemical, 25-26
- Recanalization of common duct, 255, 258
- Receding jaundice, 230
- Rectal injection of bile and bile salts, 189
- Red blood cells (*see also* Anemia; Blood; Erythrocytes)
 and bile salts, 11, 15, 62, 64, 65-67
 and biliary fistula, 264
 and cholesterol, 96, 97
 destruction of, by bile salts, 62
 hemolysis of
 by bile salts, 15, 64, 65-67
 and mucin, 16
 and intravenous bile, 8
- Regurgitation, 194; *see also* Vomiting
- Renal-dissociation jaundice, 176
- Respiration
 and bile, 11, 142-43
 in bile peritonitis, 215, 217, 218, 223
 and bile salts, 19
 and dehydrocholic acid, 272
 in jaundice, 237
 and sodium dehydrocholate, 272
 and sodium glycocholate, 272
 and sodium taurocholate, 16
- Restlessness, 218, 233
- Rheumatic pain, 144
- Rickets, 29, 265, 267, 268
- Roentgen rays
 and bile acids, 45
 and preoperative treatment in jaundice, 261
- Rotary dispersion of bile acids, 25
- Rust bile, 105
- Sadness and jaundice, 236
- Saliva
 and bile acids, 189
 bile pigment in, 55
 and bilirubin, 86
 in jaundice, 236
- Saponin, 33, 117
- Sarcoma, 259
- Sclerae in jaundice, 225, 226, 227, 236, 238, 251
- Secretine, 44
- Secretion granules, 16
- Secretions (*see also* Fluid)
 gastric, 183
 peritoneal fluid called "bile," 219
 salivary and nasal, bile acids and, 189
- Sedative action of bile, 144
- Septic hemolysis, 230
- Serosa, 19, 180-81
- Severe jaundice of Ozanam, 246
- Shells, coloring of, 91
- Sight in jaundice, 236
- Simple jaundice, 243, 246
- Sistosterin, 43
- Skeletal muscle, 10, 160-64
- Skin
 color of
 in biliary diabetes, 76
 in congenital atresia of bile ducts, 252, 253
 in icterus gravior, 251
 in icterus neonatorum, 249, 251
 in jaundice, 225, 226, 227, 236
 in obstructive jaundice, 256
 disturbances of, in pruritus, 238-40
- Small intestine and bile, 10, 183-88; *see also* Intestine
- Soaps in bile, 28
- Sodium in gallbladder, 57
- Sodium bilirubinate, 147
- Sodium chloride in gallbladder, 58; *see also* Chloride
- Sodium cholate, 27, 65
 and blood pressure, 87, 157
 and destruction of red blood cells, 64
 as detoxifying agent, 202
 and heart, 87
 and nervous system, 139, 142
 toxicity of, 11, 65, 67, 68, 69
- Sodium choleate, 27
 toxicity of, 275
- Sodium *choleini*cum, 182
- Sodium dehydrocholate, 65, 270
 and arsphenamine poisoning, 278
 and bacteria, 199, 271
 and blood, 270-71
 and blood pressure, 158

- as choloretic, 273-74, 278
- diuretic action of, 176, 275
- and heart, 271-72
- intraperitoneal injection of, 277
- intravenous injection of, 270 ff.
- and kidneys, 275
- and liver, 274
- and nervous system, 142
- oral administration of, 270, 277, 278
- and respiration, 272
- and spleen, 274
- subcutaneous injection of, 275, 276
- toxicity of, 270 ff., 275-78
- Sodium dehydrodesoxycholate, 199
- Sodium desoxycholate, 27
 - and blood, 270
 - and heart, 271
 - toxicity of, 65, 69, 156, 270 ff.
- Sodium glycocholate, 27, 33, 60, 220
 - and blood, 113, 114, 115, 117, 270
 - and blood pressure, 87, 157
 - and coagulation of blood, 127
 - as detoxifying agent, 202
 - and heart, 87, 147, 148, 152, 271
 - and intestine, 185, 186, 187
 - intrajugular injection of, 137, 138
 - intraperitoneal injection of, 213
 - intravenous injection of, 8, 138, 169, 213
 - and migraine, 278
 - and nervous system, 137, 138, 139, 141, 142
 - and peptic ulcers, 191
 - and placenta, 179
 - and respiration, 272
 - and skeletal muscle, 160, 162
 - and stomach, 183
 - toxicity of, 11, 15 f., 17, 62-63, 64, 67, 68, 69, 70, 115, 275, 276
 - and uterus, 178, 179
- Sodium taurocholate, 27, 33, 60, 72, 220
 - and blood, 15, 114, 115, 117, 121, 127
 - and blood pressure, 157
 - and coagulation of blood, 127, 135
 - and convulsions, 16
 - as detoxifying agent, 202
 - fate of, 54
 - and heart, 152
 - and intestine, 185, 186
 - intrajugular injection of, 137
 - intravenous injection of, 8
 - and nervous system, 137, 139
 - in obstructive jaundice, 256
 - and peptic ulcers, 191
 - and placenta, 179
 - and respiration, 16
 - and skeletal muscle, 162
 - and stomach, 182, 183
 - and testes, 179
 - toxicity of, 11, 17, 62-63, 64, 67, 68, 69, 70, 115, 275
 - and urine, 15
 - and uterus, 179
- Somnolence, 137, 233
- Specific gravity of bile, 12, 13, 24, 40, 62
- Spermatozoa, disruption of, by bile salts, 15, 115
- Spinal fluid, bilirubin in, 56
- Spleen
 - and biliary fistula, 264
 - in jaundice, 236
 - and sodium dehydrocholate, 274
- Spontaneous canalization, 255, 258
- Stagnant bile, toxicity of, 14; *see also* Decomposition of bile; Standing
- Standing, changes in bile on, 25, 40; *see also* Decomposition of bile; Stagnant bile
- Starvation icterus, 230
- Stasis, mechanical, 229
- Stasis icterus, 243
- Stearic acid and peptic ulcers, 193
- Stearin, 28
- Stercobilin, 55, 56
- Stercorin, 96
- Sterins, 29, 43
- Sterols, 102
- Stomach and bile, 10, 12, 182-83, 192
- Stupor, 15, 137, 235
- Subcutaneous injection
 - of bile, 12 f., 18, 123, 172, 191, 194, 220, 224
 - of bilirubin, 83-84
 - of cholesterol, 100
 - of sodium dehydrocholate, 275, 276
- Subdural injection
 - of bile, 139, 140
 - of bile salts, 139

- Subserosa, 223
- Sucrose, 121
- Sugar (*see also* Blood sugar)
 assimilation of, and cholic acid, 46
 in bile, 29-30
 inhibitory action of, on hemolysis, 121
 in urine, 166
- Sulphanol poisoning, 33
- Sulphates, ethereal, 28
- Sulphur, neutral, in jaundice, 234, 236
- Sulphuric acid salts, 28
- Surface tension
 of bile acids, and toxicity, 16
 of taurocholic acid, 25
- Surgical risk in jaundice, 259-61
- Surgical shock, secondary, 222, 224
- Sweat (*see also* Perspiration)
 bile pigment in, 55
 coloring of, in jaundice, 236
- Sympathetic nervous system, bile and,
 43, 143; *see also* Nerves; Nervous
 system
- Syphilis, 229
- Tachycardia, 146, 148, 150-51, 153, 223
- Taste
 of bile, 2-3
 in jaundice, 236
- Taurin, 17, 67, 69, 71, 106
 in bile, 69
 in blood, 69, 113
 death due to, 69
 and excretion of bile acids, 54
 in feces, 69
 and heart, 148
 and nervous system, 142
 origin of, 44
 putrefaction and, 197
 toxicity of, 8, 10
 in urine, 69-70
- Taurocholate in obstructive jaundice, 47
- Taurocholic acid, 25, 60, 69, 72, 106
 death due to, 214
 excretion of, 188
 fate of, 54
 and heart, 147
 in jaundice, 234, 236
 pK of, 26
 purity of product, 61
 surface tension of, 25
- Tears, bile pigment in, 55
- Teeth, temporary, 251, 252
- Temperature (body), 23, 236
- Terminology, 6, 21, 73
 ancient, 1-2
- Testes, action of bile on, 179
- Tests
 for bile in the urine, 166, 171
 for bile acids, 108, 109, 111, 167, 169
 for bile pigment, 108
 for bile salts, 108, 109, 111, 140, 169,
 279, 280
 for bilirubin, 88-89, 107, 108, 229, 279
 for cholesterol, 95
 for cholic acid, 21, 106
 of liver function, bilirubin as, 82-83,
 90
 for surface tension of urine, 176
 for urobilin, 92
- Tetanus, 15, 65, 137, 140, 163
- Thelykinin, 179
- Therapeutic effects of bile acids, 269-78
- Thirst, 215, 217, 255
- Thiry-Vella fistula, 184, 185
- Thoracic duct, 254
 ligation of, 255-56
- Thrombosis, 7, 11, 13, 42, 61, 80, 128,
 138, 157; *see also* Emboli
- Thyroid extract and bile excretion, 43
- Thyrotoxicosis, 58
- Thyroxin and gastric ulcers, 192
- Time of day and variation in bile, 21, 41,
 45-46
- Tissues
 action of bile on, 19
 action of bile applied directly to, 7, 19
 and bile acids, 224, 269
 bile pigment in, 56
 and bile salts, 68-69, 80
 and bilirubin, 76, 79-80, 83
 cholesterol in, 94, 96
 extravasations of blood in, 73, 76, 226,
 251
- Toxic jaundice, 243
- Toxins, 39, 102, 196-203

- Tracheal mucosa and bile salts, 19
 Transfusion (blood), 260
 Trioxystercholeonic acid, 29
 Trypsinogen, 206
 Tuberculosis, 76, 92, 93
 Tumors, small; *see* Xanthoma
 Twitching, 233
 Typhoid fever, 92, 105
 Typhoid jaundice of Leberet, 246
 Typhus, 22
 Ulcers; *see* Duodenal ulcers; Peptic ulcers
 Ultraviolet rays, 46, 267
 Unfiltered bile, toxicity of, 61
 Urea, 28, 29, 71
 Uremia, 12, 174, 246, 248, 259, 260
 Uric acid, 29, 257
 Urine
 albumin in, 113, 165, 168, 172, 176, 216, 217, 218
 bile in, 112, 165-77, 215, 216, 217, 218
 and kidneys, 166, 171-73
 and bile acids, 8, 52 ff., 113, 167, 168, 170, 174, 189, 234
 bile pigments in, 8, 9, 54, 55, 112-13, 165, 166-67, 168, 169, 170, 171, 218, 235-36
 bile salts in, 167, 169-70, 171, 176, 177, 251
 during pregnancy, 251
 and biliary fistula, 266
 bilihumin in, 166
 bilirubin in, 56, 74, 76, 77, 78, 92, 166, 167, 170, 174, 227-28, 234
 biliverdin in, 166
 blood in, 171, 172, 216, 223
 casts in, 171, 172, 177
 cholesterol in, 95, 97
 color of, 165, 166-67
 in congenital atresia of bile ducts, 253
 in feigned icterus, 225
 filtering of, and toxicity, 175
 glycocol in, 71
 in icterus neonatorum, 251
 in jaundice, 139, 165, 166, 169, 170-71, 173-77, 226, 233, 234, 236, 237
 and liver, 8, 172
 in obstructive jaundice, 8, 165, 166-67, 168-69, 170, 174, 255, 256
 output of, and bile acids, 174
 and sodium dehydrocholate, 176, 275
 and sodium taurocholate, 15
 sugar in, 166
 taurin in, 69-70
 test for bile in, 166, 171
 test for bile salts in, 140
 test for surface tension of, 176
 toxicity of, 173
 urobilin in, 93, 170
 urobilinogen in, 92, 93
 Urobilin, 32, 50-51, 75, 91-93
 in bile, 50, 92, 93
 in blood, 50, 92, 93
 daily output of, 92
 in erysipelas, 92
 fate of, 55
 in feces, 93
 and intestinal acholia, 93
 and intestine, 93
 intravenous injection of, 50-51
 and jaundice, 93
 and kidney, 92
 in leprosy, 92
 and liver disease, 92
 in lymphatic leukemia, 92
 in malaria, 92, 93
 in nephritis, 93
 in obstructive jaundice, 92
 in pneumonia, 92, 93
 in polycythemia, 92
 test for, 92
 toxicity of, 93
 in tuberculosis, 92, 93
 in typhoid fever, 92
 in urine, 93, 170
 Urobilinogen, 32, 50, 56, 92
 in bile, 92, 93
 fate of, 55
 in feces, 92, 93
 in urine, 92, 93
 Uroporphyrin, 33
 Uteroverdin, 75
 Uterus, action of bile on, 178-79
 Vaccine virus and bile, 202-3
 Variations in normal bile, 33-36; *see also*
 Diet and variations in bile; Time of day and variations in bile

- Vasoconstriction, 126
 Vasodilatation, 126
 Vegetative nervous system, bile and,
 143; *see also* Nerves, Nervous sys-
 tem
 Vella fistula, 183, 184, 185
 Veronal, 43
 Viosterol, 267
 Vitamins, 16, 28-29, 57, 58, 132, 266,
 267, 268
 Vomiting, 182, 215, 217, 218, 236, 255;
 see also Regurgitation
 Water intake by mouth, and bile, 41
 Weight, loss of (*see also* Malnutrition;
 Nutritional disturbances
 and biliary fistula, 262, 263
 in jaundice, 233
 White bile, 61, 103-4, 237
 White blood cells (*see also* Blood;
 Leukocytes)
 cholesterol in, 95
 disintegration of, by bile salts, 15
 Whole bile
 action of, on blood, 114; *see also*
 Erythrocytes
 toxicity of, 71, 141
 Wounds, effect of bile placed directly
 on, 7
 Xanthelasma, 100, 240
 Xanthoma, 96, 240-41
 Xanthophyll, 74, 75, 240
 Xanthopsia, 241
 Yellow bile, 3
 Yellow vision, 241

